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BIOLOGIC EFFECTS OF ACTIVE THYMUS AND PINEAL EXTRACTS*

A Brief Review

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IN VIEW of previous publications and articles now in press,[2,3] which report the detailed studies in determining the biological effects of active thymus and pineal extracts at the Philadelphia Institute for Medical Research, the subject will be briefly considered as a continuation of an earlier report.[1]

Briefly stated, the work of Rowntree, Clark, and Steinberg revealed accruing acceleration in development in successive generations of rats under continuous treatment with thymus extract administered intraperitoneally daily, in 1 c.c. doses, starting treatment on the fortieth to sixtieth day in the mature group and on the sixteenth to the twenty-fifth day in the prepubertal group. In the text F0 animals are referred to as the first generation and F9 as the tenth generation, respectively.

It will be noted in Table I that the average birth weight, in the controls, was 5.0 gms., but in the tenth generation, 6.0 gms.; eyes opened in the controls in fourteen to seventeen days, in the tenth generation in thirty-four to forty-two hours; teeth erupted in the controls on the ninth to the tenth day, in the tenth generation at birth; hair appeared in the controls on the fourteenth to seventeenth day, in the tenth generation on the first day; testes descended in the controls on the thirty-fifth to fortieth day, in the tenth generation on the second to the third day; the vagina opened in the controls on the fifty-fifth to the sixty-second day, in the tenth generation on the sixth day.

In the ninth generation, pregnancy occurred as early as twenty-two days with a litter being cast in forty-three days, thus establishing definite evidence of early sexual maturity; whereas, the average age at which a control conceived was eighty days to deliver at 103 days.

From the fifth to the tenth generation the young have been weaned as early as forty-eight to seventy-two hours and found to thrive as well as their litter mates left with the mother.

A step-like acceleration in growth and development has been noted in succeeding generations up to the tenth generation in which the most striking evidence was the opening of the vagina on the sixth day and the demonstration of estrus three days later, which is the accepted indication of maturity. This observation, which has never been made before, was so striking and conclusive that there can no longer be even a reasonable doubt of the cumulative effect of thymus through succeeding generations.

Many difficulties were met in determining the biological effects of thymus extract. Subsequent to the original active extracts, supplied for this investigation, variations in activity were encountered. The original extract first used at the Philadelphia Institute for Medical Research was as old as three years and was found highly potent. This extract had a pH 4.1 and was dispensed in 10 c.c. vials of lamp-blown resistance glass with low alkali content and were tightly stoppered and capped. Fresh thymus extracts were later distributed in 50 c.c. amber colored bottles of a lesser quality glass with rubber-diaphragm caps, and, though wired, were not as tight as might be. These lots of thymus extract

*Read at the annual meeting of the Minnesota State Medical Association, Minneapolis, June 24, 1935.

TABLE I. PROGRESSIVE DEVELOPMENT UNDER THYMUS TREATMENT

	Controls	F1	F2	F3	F4	F5	F6	F7	F8	F9
Average birth weight, grams	New 5.0 Old 4.6	5.1	5.3	5.3	5.6	5.5	5.6	5.5	6.5	6.0
Ears opened, days	2½-3½	2-3	2	1-2	1-2	1-2	1½-2	Birth to 1	Birth to 1	Birth to 1
Teeth erupted, days	8-10	8-9	4-6	4-6	2-3	2	1-2	Birth to 1	Birth to 1	Birth to 1
Hair appeared, days	12-16	10-12	4-6	4-6	2-3	2	1-2	1-2	1	1
Eyes opened, days	14-17	12-14	4-6	4-6	2-3	2-3	2-3	42-48 hrs.	42-48 hrs.	36-42 hrs.
Testes descended, days	35-40	15-29	15-21	10-12	6-10	4-6	3-10	3-4	3-4	2-3
Vagina opened, days	55-62	30-45	23-32	21-27	18-20	18-20	16-20	16-18	16-18	6
Pregnant, days from birth	80	70	56	42	25	40	40	37	22	—
First litters cast, days from birth	102	92	78	64	47	61	68	59	43	—

were found to range from pH 4.66-4.70. These extracts did not retain their activity and rapidly became inert.

Experiments and checks at the Philadelphia Institute for Medical Research have revealed that the active extracts of thymus contain sulfhydril estimated as glutathione. Glutathione dissolved in a dilute hydrochloric acid of pH 5.0 disappears as such in a few days, but in a hydrochloric acid of pH 2.0 it is quite stable.

By employing the following modification carried out at the Philadelphia Institute for Medical Research, an extract that retains its potency over a longer period of time is secured. At that institution the thymus extract is prepared in hydrochloric acid, 1 per cent by volume (0.4 per cent by weight), 1 gm. of raw gland to each c.c. of solution. The glands are macerated while still warm from the kill at the slaughter-house, and immediately covered with the acid above described. The mixture is then placed in a refrigerator over night,† if most convenient, before heating rapidly with constant stirring to 92 degrees C., employing about one-half hour in the process. This is allowed to settle and the clear extract siphoned off, when the residue is re-extracted in half of the bulk of the same strength hydrochloric acid, bringing the temperature to 92 degrees C. in ten to fifteen minutes.

The extract may then be concentrated by evaporating on a water bath at 60 degrees C. in a blast of air so that each c.c. represents 1 gm. of the fresh raw gland and adjusted to pH 2.0. Chlorbutol, 0.2 per cent, is used as a preservative at the Philadelphia Institute. There they also employ thymus extracts in which each c.c. represents 2 to 3 gms. of the fresh gland.

The effects obtained with thymus extracts were controlled by placing a group of animals under similar conditions on a hydrochloric acid solution of glutathione pH 2.0, equivalent to the same amount present in the active thymus extracts used. Another group, by a similar method of administration, has been treated with a hydrochloric acid extract of mesenteric lymph gland. Still another group is receiving a similarly made splenic extract and, finally, a group has been placed on combinations of glycine, cystine and glutamic acid, which are decomposition products of glutathione. Results on these experiments will appear in subsequent publications. Thus far the effects cannot be associated with the so-called thymus effect.

Subsequent to the positive findings of Rowntree, Clark and Steinberg it was found that ablation of the thymus gland in successive generations of white rats resulted in retardation in growth and development as shown by Dr. N. H. Einhorn. Administration of the active thymus extract restores these animals to normal. Thus the latter constitutes replacement therapy.

As a result of these biological studies, it is now quite evident that the effect of this thymus

†At the Philadelphia Institute for Medical Research the glands fresh from the kill are macerated at the slaughter-house and mixed with hydrochloric acid 1 per cent by volume. The mixture is then transferred in a large glass flask to the institution, where it is immediately heated to 92 degrees C. and treated as described.

activity is that of orderly, although accelerated, development to puberty and maturity, and that this effect is as striking on mentality as on bodily growth as evidenced by early weaning and maturity. With an excess of thymus, activity development becomes more marked with each succeeding generation. Rowntree and his co-workers have, so to speak, made a minute hand out of the hour hand of nature's clock.‡

The succeess attending the thymus studies prompted Rowntree and his collaborators to attempt the same procedure with pineal extracts. One of twenty pineal extracts, prepared and partly studied by the writer, in 1927, formed the basis for the preparation of the pineal extracts found active in the new study.

Effect of Pineal Extract

A small colony of four rats (Wistar strain) was started on pineal extract on March 2, 1934. At the present time the fifth generation of pineal treated rats has been reached and there are over 300 rats in the colony.

As the time is so limited, a little more detail will be brought out in the slides and the film will speak for itself. Suffice it to say that the outstanding effect is dwarfism. The young animal shows considerable variation from the normal in that it has a short snout, broad face, round head, heavy jowl and prominent eyes, giving it a "bull-dog" appearance. The body is small, the feet large, and it assumes a characteristic squat. After the first month it resembles a normal rat in miniature. At 100 to 200 days of age, these rats appear larger than their actual size due to a heavy coat of fur. Gonadal development appears earlier than bodily development. Gonadal development is quite marked in the second generation, while the precocity in bodily development does not appear until the third generation.

There is a lack of uniformity in the size and rate of growth of individuals in litters of the same and succeeding generations. The smallest animals die in several days from starvation due to inability to nurse, and loss of body heat because of the mother's neglect, in many instances. While the pineal animal is dwarfed, it grows hair and matures sexually in about one-half the normal time. These animals breed

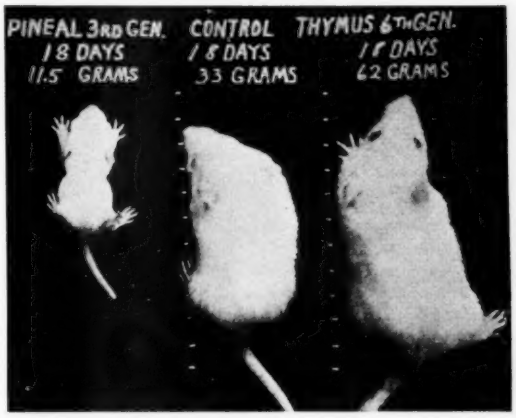

Fig. 1. Photograph of pineal, control and thymus rats, eighteen days of age.

rapidly and wear themselves out early in life. One pair of pineal treated rats that died from a respiratory infection, on the 428th day, revealed the thymus glands to be small and the adrenal glands large at autopsy; whereas, the opposite is true in the thymus treated animals. Surviving animals from pineal treated parents have weighed as low as 2.5 gms. at birth while the average birth weight of the controls was 5.0 gms.

The progressive effects on pineal treated rats are retardation in growth with acceleration in gonadal and bodily development. This suggests the clinical picture seen in pineal tumor, though the animals do not pass through a period of early accelerated growth occasionally noted in clinical conditions. There is early inactivity and weakness and it is not until fifteen to twenty days of age that these rats will climb the side of the cage or attempt to escape from a small wire enclosure. Eye anomalies have been frequently observed, with two instances of congenital hypertrophy of the eye, two of anophthalmia, and a number of cases of bilateral and unilateral congenital cataracts.

The progressive development under pineal treatment is briefly summarized in Table II.

The teeth erupted in the controls on the eighth to the tenth day, in the fifth generation

‡A clock-like precision was noted in everything up to the seventh generation and to a certain extent on to the tenth. The weight curve is in an almost identical channel from the seventh to the tenth although there is the step-like increase in the shortening of the time for the appearance of the biological phenomena. The same uniformity of results in the seventh to the tenth did not occur like were obtained up to the seventh generation because of variability and the extracts employed.

TABLE II. PROGRESSIVE DEVELOPMENT UNDER PINEAL TREATMENT

	Ears opened	Teeth erupt.	Fur app'd	Eyes opened	Testes desc'd	Vagina op'd
Controls Average	2½-3½ (3)	8-10 (9)	16 (16)	14-17 (15.5)	31-40 (38)	55-72 (65)
F1 Average	2-4 (3.3)	8-10 (9)	7-16 (13)	12-17 (14.9)	12-36 (22)	32-56 (45)
F2 Average	2-3 (2.8)	7-11 (9)	6-17 (12)	12-16 (13.8)	6-26 (15)	30-39 (37)
F3 Average	2-3 (2.3)	5-8 (6.9)	5-12 (9)	5-12 (9.8)	5-12 (10)	29-39 (32)
F4 Average	1-3 (2)	3-5 (4)	4-8 (5)	4-8 (6)	4-6 (5)	23-26 (24)

in three to five days; the fur appeared on the controls on the sixteenth day, in the fifth generation in four to eight days; the eyes opened in the controls on the fourteenth to the seventeenth day, in the fifth generation in four to eight days; the testes descended in the controls on the thirty-first to the fortieth day, in the fifth generation in four to eight days; the vagina opened in the controls on the fifty-fifth to the seventy-second day, in the fifth generation in twenty-three to twenty-six days.

An attempt is now being made to study the effect of pinealectomy in successive generations of white rats.

The pineal extract* found to be most active is that known as P-B 22. It is that fraction of a pineal picrate soluble in hydrochloric acid 0.2 per cent by volume at a temperature up to 89-90 degrees C. It is a crude extract contaminated by 0.21 per cent picric acid with a pH of about 2.0.

Controls have been subjected to intraperitoneal injections of a 0.21 per cent aqueous picric acid solution and similarly made impotent extracts without yielding the foregoing effects. Attempts are under way to refine this extract.

Conclusions

1. Thymus extract (Hanson) accelerates the rate of growth to puberty and maturity.

2. Pineal extract (Hanson) retards the rate of growth and accelerates the rate of differentiation, producing a precocious dwarf that is normal in appearance.

3. The injection of succeeding generations of parent rats has resulted in more marked demonstration of these effects.

4. The offspring of the third and succeeding generations in the thymus treated group reveal marked acceleration in the rate of growth and differentiation, while in the pineal treated group there is marked retardation in growth resulting in dwarfism, but, also, early differentiation.

5. Active pineal extracts cause early sexual stimulation as evidenced by early prolific breeding on the part of the female and enlargement of the gonads and frequent erections on the part of the male.

6. Excessive thymus activity in the early generations does not cause early cessation of breeding, nor did it cause shortening of the life span in the first generation under treatment.

7. An excess of pineal activity causes permanent dwarfism, whereas an excess of thymus active principle causes only prepubertal gigantism, the animals eventually leveling off at maturity.

*All pineal extract used in this study was prepared in the Hanson Research Laboratory aided by a grant from the Josiah Macy, Jr., Foundation of New York City.

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THE ROLE OF IRON IN THE TREATMENT OF ANEMIA*

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THE origin of our knowledge regarding iron is lost in pre-historic time. It was supposed to have been discovered by the gods, and information concerning the earliest use of iron is lost amid the myths and folklore of the ancients.

There are ninety-one Biblical references to iron, none of which mention iron as a therapeutic agent. From inscriptions and sculptures dating from the reign of the kings of the Fourth Dynasty it is believed that iron was known and used in Egypt about 3,000 years before Christ.

In the old annals of China mention is made that iron was discovered in that country about 2,900 years before Christ. The God of War, Mars, is supposed to have imbued iron with divine properties, and Greek mythology infers that iron was used in the treatment of injuries incurred during war.

The earliest authentic reference in history to the use of iron as a curative agent is found in the writings of Apollodorus, dating from about 2000 B. C. Iron rust scraped from an enchanted sword and dissolved in wine was used as the curative agent.

In the Ebers Papyrus, which dates from about 1600 B. C., mention is made of the use of iron as a drug. There are, however, no publications on iron therapy between this latter period and the contributions of Hippocrates. Beginning with Hippocrates, who frequently mentions iron in his writings, there are numerous articles on the value of iron published by eminent physicians of ancient, medieval and modern periods. During the first century of the Christian era iron seems to have enjoyed great popularity as a therapeutic agent. The Elder Pliny regarded iron rust as a valuable medicine. Nero's physician employed iron as one of the ingredients of his favorite concoction which he used to protect the Emperor's health.

Galen mentioned sulphate of iron, and used it for its astringent effect. Sydenham, the outstanding clinician of the seventeenth century, frequently mentioned iron in his writings and is one of the first to recommend using it in large doses.

Boerhaave recommended infusion of steel in wine for the treatment of chlorosis. Thomas Willis, in the seventeenth century, was probably the first to state that iron could impart color to blood. Pierre Pomet published a complete history of drugs about 1720, in which he recommended iron for chlorosis. The dose, according to this author, should be from ten to forty grams per day. As early as 1713, according to Christian, Geoffroy demonstrated the presence of iron in the ash of blood. However, Menghinis is given credit by most investigators for the discovery of iron in the blood.

More than one hundred years ago (1832) Blaud published an article in the Revue de Medicine Francaise et Etrangere in which he introduced to the medical profession his immortal pill, for which we have no better substitute, and which probably enjoys greater popularity today than it did a century ago.

In 1886, Zaleski demonstrated that iron was distributed in almost every part of the body. The fact that human tissue obtained its iron from food was probably first demonstrated by Dastre and Floresco in 1890.

The work of Whipple and his collaborators placed iron therapy on a sound foundation. From an historical point of view it is most interesting to note that Whipple, Hooper and Robscheit-Robbins used in their early experiments the historical Blaud's pill of a century ago.

Physiologic Rôle of Iron in the Body

From 1850 to 1905 investigators of iron metabolism focused particularly on the question of absorption and elimination. Since 1908, the great majority of investigations deal with iron as the component of hemoglobin. More recently a number of interesting papers has been added to the literature regarding the non-hemoglobin iron fraction, and it is now generally considered

*Read before the annual meeting of the Minnesota State Medical Association, Minneapolis, June 25, 1935.

that the liver is the storehouse for all forms of iron.

Hemoglobin is a protein compound of the pyrrol group containing chromogren with an atom of iron. It is this atom of iron which gives the hemoglobin its physical characteristics and striking color. This fact has led to many investigations on the use of iron in red blood cell and hemoglobin regeneration. Heme, which is probably the basic pigment complex, is an iron compound existing in the tissues of the body probably combined with a nitrogenous base. Iron is bound in the body with chromatin, cytochrome, and in fact with all heme pigments and is probably an essential constituent of substances concerned with oxidation.

About 70 per cent of the iron in the body is in the form of blood hemoglobin. A hemoglobin of 20 per cent is necessary to maintain life. However, Wiggers states that in repeated small hemorrhages hemoglobin may be reduced to as low as 15 per cent before life is in danger.

The daily iron requirement of the body is small; ten milligrams is probably sufficient. The average daily intake of an adult is about fifteen milligrams a day. This normal intake of iron is in the form of organic compounds which are broken down during digestion.

Absorption takes place principally in the duodenum and the iron is transmitted by the portal blood to the liver, which stores a considerable portion for future use. The availability of this stored iron is in direct relation to the metabolism of the hemoglobin. The human organism husbands its iron, using the available supply many times. Iron from broken down red blood cells is repeatedly used in the hemoglobinization of young red cells. The route of excretion is chiefly by cells of the large intestines, while a slight amount is lost through the kidneys. The amount excreted in the feces is approximately 50 per cent of the average amount ingested in food.

Anemia is produced whenever insufficient iron is ingested or when the available supply within the body is depleted.

Wiggers[31] states that "experiments on animals with controlled chronic anemias have given no evidence that increased quantities of iron exert any hemopoietic effect unless the iron reserve of the body is practically exhausted." This conclusion regarding animal experimentation is not accepted as applicable to man.

Bethell[4] and his co-workers state: "Iron deficiency anemia results from a lack of sufficient available iron for normal hemoglobin formation. Such a lack may be induced by: (1) depletion of the iron reserve from continued blood loss; (2) inadequate intake of food iron; (3) improper absorption of the element from the alimentary tract, and, as a rare possibility, (4) from inability to utilize available iron."

According to these authors the term, "iron deficiency anemia" is based on the etiologic considerations with their therapeutic implication and in no sense denotes a constant clinical entity." This clinical syndrome includes the symptoms of low hemoglobin content as well as those of any associated pathology. In many cases the deficiency is due to an abnormality in the gastrointestinal tract preventing the proper utilization of iron.

The fact that iron is present universally in plants and animals and is a necessary constituent of hemoglobin, places this metal in a vital role in all forms of life.

At this point in the discussion of iron metabolism it is in order to mention the controversial subject of copper.

Elvehjem[12,13] of the University of Wisconsin, after much experimental research, states that both iron and copper are essential for hemoglobin formation and that copper acts only in a catalytic capacity.

While copper cannot take the place of iron nor compensate for unavailable forms of iron, its function is to render the iron available after it has been assimilated.

There is considerable evidence to show that copper is an essential element of the diet and that in small quantities it is an adjuvant to iron. On the other hand, the ingestion of excessive amounts of copper is decidedly toxic.

Beard[3] and his associates are also of the opinion that copper is the catalytic agent which allows the release of iron from the liver.

The Types of Anemia in Which Iron Is Indicated

Iron has been used in all types of anemia and is probably an efficient therapeutic agent, not only in the hypochromic anemias but also as an

adjuvant to the anti-pernicious anemia factor in the hyperchromic anemias. However, its primary role as a specific agent is in the iron deficiency anemias.

Minot and Heath have shown that hypochromic anemias are much more prevalent in adults than is generally supposed.

Iron in "iron deficiency anemia" due to continued blood loss seems to be as specific a therapeutic agent as the anti-anemic factor in pernicious anemia.

In those anemias due to inadequate intake of iron in food or from the improper absorption of the element from the alimentary tract, the administration of proper amounts of iron seems to be a necessity for production of red blood cells and hemoglobin regeneration.

The type of anemia in which iron seems to have its greatest therapeutic value is where the degree of hemoglobin loss is in excess of the loss of the red blood cells, in consequence of which we have a low color index, a low volume index and concentration of hemoglobin below normal; or, in other words, a true microcytic, hypochromic anemia. In this type of anemia, iron acts as a specific.

So long as the body remains in physiological equilibrium there is probably sufficient iron available from various food sources to prevent an iron deficiency anemia.

From a physiological standpoint and from clinical experience, we may say that a diversified diet supplies sufficient iron and copper for the maintenance of blood hemoglobin in a normal individual. However, when the body has exhausted its iron storage by food deficiency or by loss of blood or other factors leading to a secondary anemia, it is exceedingly doubtful if this iron storage can be reestablished and the hemoglobin maintained at a normal level on the iron available in the food intake. Such a condition usually appears in anemia of rapidly growing children and in adults with increased hemoglobin demands as in pregnancy and frequent menstruation. Under these circumstances the diet is too low in iron and must be supplemented by the administration of sufficient iron to restore and maintain the optimum level. If the patient has a normal amount of iron, feeding of food rich in iron has no effect in increasing the hemoglobin content.

Babies born of anemic mothers have a deficiency of iron storage in the liver during intrauterine life and will be anemic. This anemia cannot be relieved by simply prescribing food rich in iron, but iron itself must be prescribed in sufficient amounts to restore the iron reserve.

Until quite recently it was thought that all the iron in food material could be utilized by the body; however, hematin iron, while available in food, cannot be assimilated.

In the treatment of anemias with very low hemoglobin content, foods rich in iron cannot supply enough of this metal to promote rapid regeneration and hemoglobinization of red blood cells.

It is not necessary to prescribe copper before it is determined that iron alone is ineffectual. If the patient fails to respond to adequate doses of iron it is reasonable to supply copper in the hope of obtaining a release of stored iron.

Therapeutics

A review of the literature shows that the style of usage of iron changes rapidly: at one period, organic iron; at another period, inorganic iron, and, as the pendulum swings, soluble iron and ferro and ferri salts of iron, even to the clinical use of so-called magnetic and inactive non-magnetic iron.

As important as iron is to life, it is amazing how little the body contains. According to Ottenberg, the total amount of iron in the human body is about 3.5 grams, or less than the weight of a five cent piece, and 2.5 grams of this iron is in the form of hemoglobin.

While the total amount of iron in the body is small, it is an element essential to life.

One of the important points which has recently been brought to the attention of clinicians is the necessity of prescribing iron in large enough quantities for the human body to absorb a sufficient amount.

It should be definitely stressed that to get a hemoglobin increase by the administration of iron it is necessary to give an enormously large daily dose in order that so small a quantity as one-quarter grain of metallic iron may be assimilated and used as a building stone for hemoglobin formation in anemia.

If it is correct to use the term "iron deficiency anemias" the reticulocyte response to iron may be due to the direct stimulating effect of

this drug on the hemopoietic system. While in severe forms of anemia following blood loss the reticulocytosis and red blood cell regeneration may be dramatic, the reticulocyte increase is not as great as the response following the administration of the anti-anemic principle in pernicious anemia nor is the return of the red cells to normal as rapid.

It is well known that only a small percentage of iron ingested is absorbed, and other routes of administration have been advocated but up to the present time the parenteral administration of iron has not proven therapeutically efficacious.

The clinician should bear in mind the content of metallic iron in the preparation he uses. Reduced iron contains 90 per cent, while ferric ammonium citrate contains only about 16 per cent of metallic iron.

It has been emphasized by Witts and Robscheit-Robbins that there is an optimum level at which iron may be stored in the body and also that there is an optimum dosage above which it is needless to go.

We should seek this optimum dose by the same criteria we now use when we administer the anti-anemic principle of liver for pernicious anemia. These criteria are the increase in reticulocytes, the increased number of red blood cells and the increased percentage of hemoglobin following the therapeutic use of iron.

The rapidity with which the hemoglobin and reticulocytes increase seems to depend upon the initial red cell count and hemoglobin estimation. When the count is very low and the hemoglobin is reduced to a greater extent we may expect a fairly marked and rapid increase in the outpouring of reticulocytes and hemoglobin under adequate dosage of iron. As we approach the normal level the increase is not so rapid. Therefore, the optimum dose may have to be continued over a long period. The reticulocyte response begins on the third to fifth day, reaching its height quickly and persisting for about seven days, slowly returning to its normal level.

It appears to be the consensus of opinion that the necessity for large doses of iron lies in the difficulty with which this metal is absorbed from the gastrointestinal tract.

It has been established that hydrochloric acid in the gastric contents favors the absorption of iron.

The exact mechanism by which iron produces an increase in hemoglobin and an increase in red blood cells is at present not definitely known. The weight of opinion is that in the administration of iron we are supplying a substance which is deficient and which cannot be synthesized in the tissues.

Iron can be administered effectively in all forms of the so-called secondary anemias, and the presence of definitely known causes of anemia, such as carcinoma and tuberculosis, is not a contraindication to the use of iron.

Individuals who have suffered from secondary anemia over long periods of time may require prolonged iron medication before the initial response is obtained.

The danger of overdosage with oral administration of iron is slight. The total daily dosage of iron is fractionated and the proper fraction administered at least three times daily, preferably at meal time.

It is confusing to search the literature for authentic information regarding the best preparation of iron to use. A multitude of preparations have been proposed. In fact, nearly every preparation of iron known to pharmacy has been administered, some authors advocating the ferrous salts, while others are equally emphatic in stating that ferric compounds are superior preparations. To the experienced physician it seems to make little difference which preparation of inorganic iron is prescribed provided it is given in adequate dosage with the proper distribution of the dosage during the twenty-four hour period.

Without attempting to enumerate all the preparations of iron which have been proposed, we may state that for practical purposes the following preparations in the order given are probably the best both from the standpoint of the tolerance of the patient and from the hemoglobin response and red blood cell regeneration.

1. Reduced iron or ferrum reductum which contains 90 per cent of iron, thus necessitating a daily optimum dose of 1.5 grams.

2. Ferris ammonium citrate which contains 17 per cent of iron and requires a daily dose of 6 grams.

3. Saccharated ferrous carbonate in powdered form which contains 15 per cent of iron carbonate and necessitates a daily dose of 10 grams.

4. Ferrous carbonate in the form of the historical Blaud's pill which contains 60 milligrams of iron carbonate and requires a daily dose of seventeen pills.

Ferric ammonium citrate may be given in solution or in capsules and is well tolerated by children.

Saccharated ferrous carbonate is preserved with sugar and is non-irritating and non-astringent, which makes it an admirable preparation of iron.

Ferrous carbonate in the form of Blaud's pill requires a large number to secure the optimum dose and is an excellent form of iron where frequent administration is necessary.

In patients who have active peristalsis or insufficient hydrochloric acid in the stomach, the frequency of dosage should be greatly increased even to the point of hourly doses so that iron may be present in the duodenum almost continuously.

If the clinician obtains a quick and dramatic response from the initial treatment with iron he may regard this as a good prognostic sign. The condition of the patient's gastrointestinal tract must be taken into consideration. Rapid transit through the gastrointestinal tract hinders absorption and requires repeated doses until the diarrhea has been controlled. Gastroenterostomies may not permit of sufficient iron being absorbed in the duodenum. If achlorhydria is present deficient absorption may occur.

From a review of the literature and from our personal experience it seems that the optimum daily dose of iron, as metallic iron, will fall between 1 and 1.5 grams daily. Therefore the percentage of iron in the preparations prescribed must be known in order that one may compute the proper dose of the preparation. The distribution of this amount during the day must be given careful consideration as repeated doses are more efficacious than a single dose.

Reduced iron is small in bulk and non-irritating and is a very satisfactory preparation.

Summary

In this brief summary of the knowledge of iron in the treatment of anemia, I have attempted to trace man's knowledge of this metal from its first historical mention to its present application as a therapeutic agent.

The metabolism of iron has been discussed with special reference to its physiological role in the formation of hemoglobin. We have attempted to summarize the present known facts in regard to the assimilation, utilization and excretion of iron.

A brief summary of the types of anemia with the response to be expected and the criteria of optimum dosage has been given. The preparations available, their efficacy and method and frequency of administration have been pointed out.

Conclusions

1. Iron is necessary to tissue metabolism.
2. Iron is necessary to hemoglobin formation and probably red blood maturation.
3. Iron is a specific therapeutic agent in the secondary anemias of the iron deficiency type.
4. Iron produces a definite reticulocyte response and hemoglobin increase in practically all types of anemia except pernicious anemia and in this disease it is an adjuvant to liver therapy.
5. The daily optimum dosage of metallic iron for the adult falls between 1 and 1.5 grams.
6. Fractionated doses spread over the day have been demonstrated to be more efficacious than a single daily dose.
7. The potency of a preparation in iron content may be measured by the reticulocyte, red blood cell and hemoglobin increase.
8. When the optimum dosage of iron has been reached increased dosage above this point has no effect.
9. There is little danger from over-dosage of iron when given by the oral route.
10. Iron has been proven an efficient therapeutic agent in the anemias of infancy and those anemias accompanying the physiologic states of pregnancy and menstruation.

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THE ROLE OF DRUG ALLERGY IN THE ETIOLOGY OF PRIMARY GRANULOCYTOPENIA*

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THE syndrome first described by Schultz,[51] in 1922, under the name of agranulocytosis and by Friedmann,[22] in 1924, under the name of agranulocytic angina has two principal clinical features: severe granulocytopenia and evidence of bacterial invasion of varying extent. For a time it was felt that bacterial invasion, resulting in angina and fever, was the primary manifestation and that the granulocytopenia was secondary to it and the result of overwhelming sepsis. Early studies of the etiology, therefore, were directed toward establishing various bacteria found in the mouth and throat or in the blood stream as the direct cause of the disease. More recently, however, it has been adequately established that granulocytopenia is the primary manifestation and that the bacterial invasion is secondary to and made possible by the extreme depression of the granular leukocytes. Consequently etiologic studies have been directed toward agents or mechanisms capable of a sufficiently selective effect on the granulocytes to produce a neutropenia of the type observed.

It was shown by Kracke[37] that it was possible to inject benzene into rabbits in such small doses that it exerted a selective affinity for granulopoietic tissues, leaving the erythrocytic and erythroblastic elements undisturbed. Larger doses of benzene produced inhibition of all cellular types. Arsphenamine also has long been known to produce bone marrow depression frequently, usually, however, with anemia and thrombopenia in addition to reduction in granulocytes. Dodd and Wilkinson[17] reported a case of typical agranulocytic angina which followed sulpharsphenamine therapy and tabulated twenty-four cases from the literature. However, of these, only sixteen showed significant reduction of granulocytes and eight were recorded as having severe anemia in addition. Farley[18] reported a series of cases of depressed bone marrow function following arsphenamine treatment, of which three presented the clinical picture of granulocytopenia. Groen and Gelderman[24] observed two cases in which the appearance of agranulocytosis so directly followed salvarsan treatment that an accidental relationship was felt by them to be untenable. Reports of blood dyscrasias following the use of various arsenicals, especially arsphenamine and neoarsphenamine are relatively common in the literature and the frequency of associated skin lesions is suggestive that an allergic drug reaction is present in many cases at least. Stratton[56] cited an extremely interesting case in which following the fourth injection of neosalvarsan the patient developed extreme pallor, sore throat, fever and leukopenia of 2,000 cells per c.mm. with 1 per cent granulocytes. Hemorrhagic bullæ appeared on the skin. After six days there was definite improvement and by the twenty-second day recovery was complete. One month after the reaction treatment was re-

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sumed using pentavalent tryparsamide instead of the trivalent neosalvarsan with no further trouble.

Granulocytopenia has been described following the use of stovarsol,[6] after acetylarson,[10] and after pure inorganic sodium arsenite.[63] It has also been reported by several authors following the use of various preparations of bismuth.[5, 44, 53, 60] Injections of certain preparations of gold salts have produced the clinical picture of malignant neutropenia.[1, 2, 4, 9, 11, 21, 29, 32, 49] Vonkennel[61] observed the agranulocytic blood picture after the injection of a gold oil, and made the significant observation that intense itching may be a premonitory symptom of granulocytopenia.

Many of the neutropenias which have been observed after administration of the drugs mentioned show accompanying anemia or pancytopenia which excludes them from the primary granulocytopenias if one is to regard the latter as a distinct disease entity, although the fundamental mechanism of production may be similar. The extreme leukopenia seen as a part of overwhelming sepsis, in aleukemic leukemia, aplastic anemia, certain metastatic bone tumors, and as the result of the direct myelotoxic action of certain drugs such as benzene in which the severity of the lesion varies directly with the amount of the drug ingested or encountered represents an entirely different phenomenon.

In 1933 we presented evidence[41] to show that in certain instances at least the use of amidopyrine or amidopyrine-containing drugs directly preceded the onset of primary granulocytopenia so that an etiologic relationship to the disease seemed probable. To our last reported[42] series of twenty patients of whom all but one (who took an unidentified drug) were known to have taken amidopyrine prior to the onset of illness, two more are added.

Case Reports

Case 21.—T. S., male, aged fifty. Until August, 1934, when he developed a corneal ulcer, there had been no illness. Subsequently, for the relief of pain, allonal (allyl-iso propyl barbituric acid plus amidopyrine) in an unknown amount had been taken at intervals over a period of four weeks. On October 2, 1934, he became acutely ill with a chill, sore throat and fever of 103°. When seen October 4 there was no definite angina, but the white cell count was 2,000 with granulocytes absent. He became steadily worse and died on the eighth day, no granulocytes having been found at any time.

Case 22.—S. B., a housewife, aged fifty-two, was admitted to the Milwaukee County Hospital for the third time December 1, 1934, because of chronic infectious arthritis of fifteen years' duration. Thyroidectomy had been done in 1919 and salpingectomy and appendectomy in the same year. In 1921 she had a sinus operation, in 1925 all teeth were extracted and in 1928 a tonsillectomy was done. From January 29, 1935, to March 12 she received amidopyrine gr. 10 (0.6 Gm.) daily and from February 2 to March 12 amytal compound gr. 10 daily in addition. On March 11 ulceration developed on the lower gum and sores appeared in the mouth, nose and vagina. The temperature, which had been between 98 and 99, rose to 100 and on March 12 the blood count showed 1,150 leukocytes with 100 per cent lymphocytes; erythrocytes 4,500,000; hemoglobin 68 per cent. She was given pentnucleotide 10 c.c. on March 13, and on March 14 the leukocytes were 2,250 with 94 per cent lymphocytes and 6 per cent monocytes. On this day, by error, she was given 10 gr. of amytal compound. The following day, March 15, her white cell count was 1,550 and on March 16 it fell to 700. She was given a transfusion of 500 c.c. of blood. On March 18 the white cell count was 1,800 with 9 per cent rods; 4 per cent segmented cells; 67 per cent lymphocytes; 18 per cent monocytes and 1 per cent eosinophils. During the next eight days the leukocytes gradually increased and on March 27 the white cell count was 6,300 with 64 per cent polymorphonuclears. On March 28 there was a chill and temperature rise to 104°. The following day the white cell count was 14,700 with 74 per cent polymorphonuclears; R.B.C. 5,200,000; Hb. 81 per cent. The temperature and white count remained high and on April 2 there was another chill, a temperature of 105° and evidence of pyelitis. On April 3 she developed thrombophlebitis in the right leg and the white cell count rose to 53,000 with 88 per cent polymorphonuclears; 10 per cent lymphocytes; 2 per cent mononuclears; R.B.C. 4,600,000; Hb. 88 per cent. On April 5 and 6 abscesses developed successively in the left and right thigh. On April 9 the white cell count was 19,000 and on April 16 was 27,100 with polymorphonuclear counts of 92 and 96 per cent respectively. On April 16 a perinephritic abscess developed and she died April 21 of septicemia.

In this patient not only did the use of amidopyrine directly precede the onset of granulocytopenia but a characteristic depression of the leukocyte count followed the erroneous administration of 10 grains of amytal compound after evidence of some clinical improvement had appeared. In spite of the severe neutropenia which followed, twelve days after the extreme granulocyte depression the onset of a septic infection was followed by a normal granulocyte response with marked leukocytosis. It seems obvious that no underlying bone marrow insufficiency could have played a rôle in the development of the acute primary granulocytopenia in this patient.

Other reports of the onset of primary granulocytopenia following the use of amidopyrine have continued to appear in the literature and at the

present time thirty-three authors have reported that the use of amidopyrine or amidopyrine-containing drugs preceded the onset of the disease and apparently was a causal factor in 163 out of 263 patients reported by them (Table I). In addition other drugs were reported as having a known or probable causal relation to the onset in thirty-nine additional patients, bringing the total number in this group in which a drug etiology was probable to 202.

Jackson and Parker[31] have pointed out that the mere use of a drug directly prior to the onset of illness is by no means satisfactory evidence of a causal relationship. While in seven of the twenty-seven cases studied by Jackson[30] amidopyrine seemed definitely related to the onset of granulocytopenia, eight other patients "had taken amidopyrine or allied compounds in considerable quantities, yet it could be shown in these instances that the therapy had not the slightest causal relation to the actual disease" since recovery took place in spite of continued administration of the drug.

We are entirely in accord with this attitude. However, it must be emphasized that positive demonstration of a causal relationship is our immediate concern and the accumulated evidence leaves little room for doubt that amidopyrine and certain other drugs, all of which are known to be frequent causes of allergic drug reactions, can produce in sensitive individuals the clinical picture of primary granulocytopenia. This allergic drug reaction represents an entirely abnormal response to the drug and is not in any way a heightened physiologic response. While benzene and similar leukotoxic drugs are capable of producing bone marrow depression in normal toxic doses, the mechanism responsible for the appearance of primary granulocytopenia following drug administration is entirely different. In many instances there is a history of long continued use with no ill effect, and then, after a temporary cessation of use, readministration of a relatively small amount of the drug is followed by the dramatic onset of the disease.

We have previously reported[55] recurrences of granulocytopenia in two patients both of whom had developed the disease following the use of amidopyrine. The first patient, a physician, had been in the habit of using allonal (allyl-isopropyl barbituric acid with amidopyrine) frequently for insomnia. Following recovery in November, 1931, from the original typical granulocytopenia he had two sharp recurrences on May 17 and July 5, 1932, each of which was later found to have immediately followed the taking of amidopyrine. After an interval of ten months during which time the white count remained normal, a single 5 gr. tablet (0.3 Gm.) of amidopyrine was taken. Within three hours there was deep seated bone ache, malaise, fever of 102° and a rapid fall in granulocytes to 250. Subsequently the count gradually rose to reach the normal level within six days. On December 12, 1932, a patch test using a 10 per cent suspension of amidopyrine was applied to the unabraded skin. Twenty-four hours later he complained of tiredness, aching of the bones, chilly sensations and his temperature was 102°. The patches were immediately removed and at this time the white count was 5,450. Four hours later it was 3,550 and the following morning, thirty-six hours after the patches were applied, it was 2,700. During the next forty-eight hours the count gradually returned to the normal level of 7,200.

Similar results were reported in a second patient with chronic infectious arthritis who developed granulocytopenia while under observation in the Milwaukee County Hospital after medication with amytal compound (amytal with amidopyrine). Following recovery, recurrences were induced by giving a single 10 gr. capsule of amytal compound, by a 5 gr. tablet of amidopyrine alone, and by the application of an amidopyrine patch test to the unabraded skin. Administration of amytal alone was followed by no change in the total or granulocyte count.

Grant[23] reported a patient with arthritis who had taken amidopyrine regularly for several months and discontinued the drug on admission to a hospital for cholecystectomy. During convalescence she was given a sedative containing amidopyrine and a few hours later had a chill, followed by unexplained fever. No blood count was made. A few weeks later she again took amidopyrine and immediately had a chill and rapid rise of temperature. On the following morning her leukocyte count, which had been normal four days previously, was 2,000 with 2 per cent granulocytes.

de Vries'[16] patient had four recurrent attacks each in connection with the use of amidopyrine or amidopyrine-containing preparations. On one

TABLE I. GRANULOCYTOPENIA FOLLOWING AMIDOPYRINE MEDICATION

Author	Reference	Total Cases	Preceded by Amidopyrine Alone or Combined	Preceded by Other Drugs	Remarks
Anderson, S.	3	1	1		
Benjamin & Biederman	7	1	1		Recurrence on readministration.
Corelli, F.	12	2	2		
Costen, J. B.	13	3	2		
de Vries, S. I., Jr.	16	1	1		Four recurrent attacks, each after amidopyrine.
Fisher, J. H.	19	1	1		
Fitz-Hugh, T. Jr.	20	26	17		
Grant, S. B.	23	1	1		
Groen & Gelderman	24	20	14	6	
Hench, P. S.	25	1	1		
Hoffman, Butt & Hickey	27	14	13	1	One case developed under observation.
Holten, Nielsen & Transbol	28	6	6		All developed under observation.
Jackson, H., Jr.	30	27	7		Eight others continued to take amidopyrine during acute illness without apparent harm.
Johnson, W.	33	1	1		Two recurrences after amidopyrine.
Jorgensen, H. K.	34	1	1		
Knudson, O.	36	1	1		
Kracke & Parker	38	11	6	5	
Larsen, B.	39	1	1		
Madison & Squier	42	23	21	2	Recurrences after patch tests and after ingestion in two.
McGuire, J.	40	1	1		
Moltke, O.	43	1	1		
Phillips, E. W.	45	3	3		
Plum, P.	46	7	7		Symptoms reproduced on readministration in one.
Randall, C. L.	47	1	1		Developed under observation.
Rawls, W. B.	48	2	2		Recurrence on readministration in one.
Roche, F. W.	50	1	1		Recurrence on readministration.
Seeman, H.	52	36	13		Amidopyrine not given in fifteen.
Sturgis & Isaacs	57	9	7		Neutropenia induced on readministration in three patients.
Videbech, H.	58	1	1		
von Bonsdorff, B.	59	3	3		
Watkins, C. H.	62	53	22	25	Recurrences after barbiturates.
Zinberg, Katzenstein and Wice	64	1	1		Recurrence on readministration.
Zinninger, P.	65	2	2		
TOTAL		263	163	39	

occasion the onset of a new attack occurred with a chill which followed within a few hours the use of the drug.

Benjamin and Biederman[7] gave their patient 10 gr. of amidopyrine seven months after recovery. One hour after the drug was taken headache, nausea and backache developed gradually followed by fever and a fall in the leukocyte count from the previous level of 3,700 to 1,700 at the end of three hours. On the following day the count was 1,000, after which it gradually rose to 4,400 on the fifth day and 5,200 on the ninth day. Similar administration of aspirin or allurate (allyl-iso-propyl barbituric acid) caused no change in the count, and intracutaneous, patch tests and passive transfer tests with aspirin and amidopyrine were all negative.

One of Rawl's[48] patients who had developed neutropenia after taking amidopyrine returned to normal nine days after the drug was omitted, without any other form of treatment. After a period of rest resumption of amidopyrine was again followed by neutropenia after about 280 grains (18.2 Gm.) had been taken, and again with omission of the drug the leukocyte count returned to normal in eight days.

Zinberg, Katzenstein and Wice[64] observed the onset of granulocytopenia after the use of amidopyrine in a patient who had recovered from pneumonia. After uneventful recovery from the

granulocytopenia, 5 gr. of amidopyrine was given at 1:30 p. m. At 2:45 p. m. the patient had a severe chill lasting fifteen minutes with a subsequent rise in temperature to 101.4° F. At 2:55 p. m. the white count was 4,600 and at 3:45 p. m. was 1,300. The following day it was 2,200 and by the fourth day had returned to the normal level of 7,800.

Plum[46] reproduced the clinical picture of granulocytopenia in a patient whose original attack had followed the use of amidopyrine combined with diallylbarbituric acid. After the white cell count had returned to 9,020 with 63 per cent granulocytes 0.2 Gm. amidopyrine was given by mouth. An hour after the drug was taken the patient felt indisposed and there were "shiverings" of the extremities aggravated during the next six hours. At the same time there was elevation of temperature. One and one-half hours after taking the drug the white cell count fell to 1,900. This initial fall was followed during the next three hours by a rise to 11,500, after which the count again fell during the next 24 hours, at first rapidly and then more slowly, to 2,000 cells per c.mm. Through the next eight days the count gradually increased to reach 10,400 on the tenth day.

Roche[50] administered a single 5 grain tablet of amidopyrine to a recovered patient whose initial granulocytopenia had followed the use of this drug. Within an hour there was a chill, elevation of temperature and a fall in the white count from the previous normal level to below 2,000 cells per c.mm. A gradual, uneventful return to normal followed.

Sturgis and Isaacs[57] reported oral administration of amidopyrine in a dose of 0.3 to 1.0 Gm. to three of their recovered patients. A drop occurred in the total and granulocyte count in each of the three patients and with two of them the test was repeated with similar results. One patient who showed a drop with amidopyrine failed to do so when tested with 0.3 Gm. of barbital.

Allergic drug reactions are known to occur after the use of barbiturates. We personally have observed no cases of granulocytopenia following the use of these drugs. However, Watkins[62] has reported seventeen cases in which barbiturates alone were used prior to the onset of illness. Eight patients had taken amytal or sodium amytal. One patient who had recovered from an attack "probably induced by amidopyrine" developed a typical recurrence within 48 hours after receiving amytal for insomnia. Four months later, of her own accord, she took 6 gr. of sodium amytal for insomnia and a third granulocytopenic phase developed from which she died in twelve days. Another patient who had recovered from two attacks each apparently induced by amytal four months later took of his own accord 1½ gr. of amytal. Within thirty-six hours the leukocyte count had dropped to 1,800 with 1 per cent neutrophiles. Rapid recovery followed. Seven patients in Watkins' series took pentobarbital sodium prior to the onset. All seven of these patients were known to have had normal blood counts prior to use of the drug and no other drug was taken. Two patients took phenobarbital and one had a dermatitis in association with the leukopenia. One patient had taken acetanilid; six took an unknown sedative for headache, and six patients, all of whom recovered, gave no history of drug usage prior to the onset of the granulocytopenia.

Following the introduction of dinitrophenol and its rather wide use for weight reduction this drug also has appeared in apparent etiologic relationship to the onset of granulocytopenia. Hoffman, Butt and Hickey[27] reported granulocytopenia with recovery in one of their patients after two weeks ingestion of the drug. Silver[54] reported a fatal case in which dinitrophenol was taken before the onset, but causal relationship was not positively demonstrated. Two additional cases were reported by Damoshek and Gargill,[14] one case was reported by Davidson and Shapiro,[15] one by Watkins[62] and one by Bohn.[8] We have recently observed an additional case in which dinitrophenol was taken prior to the onset of the illness, but as yet we have not felt it safe to verify the causal relationship by ingestion or patch tests.

The extreme difficulty of obtaining an accurate history of medication preceding the acute illness was well illustrated by this case. During the acute period and for some time after recovery the patient constantly maintained that no drugs whatever had been used and it was only after repeated questioning that the use of dinitrophenol was admitted. The futility of attempting to obtain a history of previous medication months or years after an attack of granulocytopenia is obvious.

This rapidly growing evidence from independent observers leaves no room for doubt that a single small dose of certain drugs, especially amidopyrine, will, in the sensitive individual, produce a profound fall in both the total and granulocyte counts and, in the more severe reactions, the clinical picture of primary granulocytopenia. Kracke and Parker[38] have advanced the hypothesis that the depression of the granulocytes after amidopyrine and similar medication is the result of a direct toxic action on the bone marrow of some of the oxidation products derived from benzene and they were able by the use of such oxidation products to depress the leukocyte count in an occasional rabbit to as low as 1,000 cells per c.mm. Because among the thousands of persons taking "benzamine" drugs such as amidopyrine only the occasional individual is affected, they assumed "the existence of a previously weakened, damaged or idiosyncratic bone marrow." If this assumption were true then it would seem logical to expect a person who had had granulocytopenia due to amidopyrine subsequently would show a marked leukopenic reaction when given drugs such as arsphenamine, acetanilid or phenacetin which they have shown ultimately yield these common oxidation products. We have observed no such reaction, at least after the use of phenacetin by some of our patients. Furthermore our recovered cases have shown subsequently an entirely normal bone marrow response without evidence of impairment in function as long as the drug concerned was avoided. Herz[26] has intimated that the granulocytopenia following amidopyrine resulted from the toxic effect of the imido (NH) radicle, derived from phenyl hydrazine, which resembles the latter in its rapid reduction of granular leukocytes in the blood stream. This conception again presupposes direct toxic action on the bone marrow for which there is no supporting evidence.

We believe that the neutropenias seen following the use of amidopyrine and similar drugs are the result of an allergic drug reaction and not to a heightened pharmaceutical or physiological response. The frequently associated chill and temperature rise are common symptoms of allergic drug reactions in general[35], and it is also well known that in such reactions leukopenia is often present just as in serum disease. The extremely minute amount of drug effective in producing a reaction after the application of patch tests in two of our patients, together with the absence of acceptable evidence of bone marrow damage in the thousands of persons who have taken amidopyrine without the slightest evidence of ill effect, can be explained on no other basis. How such sensitivity develops and whether the sensitivity is temporary or permanent are questions that can not be answered at the present time. Just as varying degrees of sensitivity to proteins are observed clinically in atopic diseases, sometimes being so great that even a cutaneous test results in a violent general reaction and at other times so mild that only massive contact will upset allergic equilibrium and cause symptoms, so we believe varying degrees of sensitivity may exist to amidopyrine and similar drugs. Skin tests in drug hypersensitvity are usually negative but as in all allergic phenomena negative skin tests do not exclude the existence of the hypersensitive state. In our two patients a slight hyperemia was noted from the amidopyrine patches, definite enough to be correctly read by three independent observers, but thus far corroborative positive reactions have not been obtained by others, and no one has obtained positive tests after passive transfer.

We know of no way of recognizing in advance those individuals who may develop drug idiosyncrasy. However a history of drug intolerance of any kind demands increased vigilance. We have seen two patients who gave a history of aching in the legs, malaise and general discomfort after taking amidopyrine sufficiently pronounced that its use had been discontinued by both. Unfortunately, permission for blood studies after experimental ingestion of the drug could not be obtained. The well known fact that sensitivities can and do develop to many valuable drugs such as aspirin, morphine, quinine, salvarsan, etc., by no means precludes their use. Recognition of the fact that such idiosyncratic reactions are possible should simply be an added safeguard for intelligent use. Because of the undoubted frequent association of granulocytopenia with amidopyrine medication repeated blood counts and close observation of clinical symptoms are absolutely essential during administration of this drug and we feel strongly that the use of amidopyrine or drugs of

a similar nature during acute primary granulocytopenia is absolutely contraindicated, even though the clinical evidence in a given case may not seem to indicate any direct relationship to the onset of the disease.

Summary

1. At the present time thirty-three authors have reported the use of amidopyrine or amidopyrine-containing drugs preceding the onset of acute primary granulocytopenia in 163 out of 263 patients, while other drugs had a known or probable causal relation to the onset in thirty-nine additional patients, bringing the total number in the group in which a drug etiology was probable to 202.

2. Granulocytopenia following drug administration must be the result of an allergic rather than toxic response since the drugs concerned have been taken by normal individuals in massive doses over long periods of time with no observed effect on the total or granulocyte counts, and the incidence of primary granulocytopenia is extremely low as compared to the widespread use of these drugs. Furthermore granulocytopenia has been elicited repeatedly in recovered amidopyrine-sensitive patients by readministration of amounts of the drug so minute that a toxic action is inconceivable. In addition, the severity of the granulocytopenic reaction and subsequent recovery of normal granulopoiesis does not seem to bear any direct relation to the amount of drug used. Patients who have recovered show a normal bone marrow response toward subsequent ordinary stimuli and do not have recurrences unless a specific drug to which hypersensitivity exists is taken again.

3. Just as the allergic reaction to aspirin results most frequently in hives or violent asthma, so it appears that the allergic reaction to amidopyrine is especially manifested by extreme neutropenia. The same granulocytopenic reaction, however, can and does occur to other drugs, and possibly to some protein allergens as well. When such is the case, administration of amidopyrine during the disease or after recovery has no effect on the granulocyte count.

4. The extreme difficulty of obtaining an accurate history of medication preceding the acute illness even at the time of illness, and the absolute futility of attempting to determine accurately such a history from hospital records, are apparent. Countless preparations are marketed under names giving no suggestion of their amidopyrine content.

5. The very nature of the allergic drug reaction with its associated malaise, deep-seated bone ache and fever is such that readministration of anodynes such as amidopyrine is usual. Amidopyrine and allied drugs are chiefly dangerous, therefore, when the possibility of the allergic reaction is not recognized. In the normal individual they may be used with safety, but their use requires close clinical observation checked by blood counts for evidence of hypersensitivity, and immediate avoidance of the drug if even suggestive neutropenia appears. Self medication obviously is especially hazardous. Although we recognize that certain patients can take amidopyrine during acute primary granulocytopenia without apparent ill effect, it is our opinion that drugs of the amidopyrine type should never be employed during the acute phase of the disease.

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THE LABORATORY DIAGNOSIS OF THE VARIOUS FORMS OF DYSENTERY*

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ALTHOUGH various forms of dysentery were clearly described by Hippocrates and probably existed for centuries before the time of Christ, knowledge of these conditions really dates from the discovery of the group of dysentery bacilli first reported by Shiga in 1898. Although amebas had been found before this time, and although Koch, in 1883, had been impressed with their presence in intestinal ulcers, it was not until Shiga's discovery that it was possible to make definite scientific headway in study of dysentery. In spite of the work of Kartulis, Councilman and Lafleur, Schaudinn, and others, knowledge of dysentery was rather chaotic until about 1913.

By the term "dysentery" one means a symptom-complex identified by characteristic stools and characteristic pain. The stools are small, are frequently passed, and contain mucus which is usually greenish yellow or dirty brown, because of the altered blood that is mixed with it. The mucus may be mucopurulent, there may be streaks of blood on it, or spots or pools of blood may be present. The masses of mucus may be suspended in serous, sanguineous or fecal material, and sometimes the discharges are watery. Although, as compared with the stools of dysentery, diarrheal stools are as a rule more copious and passed less frequently, they may, and often

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do, contain microscopic or occult blood and some mucus. The distinction, although evident in typical conditions, is more artificial than real in some others and frequently dysenteric stools alternate with diarrheal stools.

Blood resulting from hemorrhoids and anal fissures may sometimes confuse the examiner. Its very fresh appearance, its ability to clot, the history of the patient, and physical examination of the rectum and anus must be taken into account in determining the true significance of the presence of such blood.

The characteristic pain is termed "tormina" and "tenesmus." Tormina, the griping, colicky pain which centers about the umbilicus, is more likely to accompany lesions about the cecum, while tenesmus is increased as the lesions encroach on the rectal region. This painful, spasmodic contraction of the anal sphincter gives the feeling of incompleteness of defecation, and leads to straining, which justified Manson's expression "glued to the commode."

Frequently the only means of positive diagnosis of the type of dysentery is laboratory examination of the discharges of the patient, and no group of diseases requires more cooperation between the laboratory and the clinician. I shall confine my discussion to clinical laboratory procedures which are direct and practical and which have been fairly well standardized.

Chronic Ulcerative Colitis

One is limited entirely, from the laboratory standpoint, to a study of the feces in the diagnosis of chronic ulcerative colitis. As a rule, the patient's bowel movements are frequent and foul smelling. They are characterized by the presence of a large amount of pus, which frequently can be detected with the unaided eye from its grayish white appearance. The feces may or may not contain gross blood, and sometimes the blood may be bright red, indicating hemorrhage near the rectal region; there is a minimum of mucus. The movement as a whole is typically soft and unformed but not watery. Microscopically, the large amount of pus and relatively small number of erythrocytes are striking; Charcot-Leyden crystals are, almost without exception, abundant.

Whether it is correct to state that a diagnosis of chronic ulcerative colitis is justified when the diplococcus described by Bargen is found in the feces or is obtained from the ulcers is still a matter to be conclusively settled. The organism has been found and reported by others in a variety of conditions, but it is certainly found in a large percentage of cases of chronic ulcerative colitis, and, because it adds some weight to the diagnosis, it should be sought. If vaccines or serums are to be used for treatment the organism must be isolated.

The best procedure is to obtain material from a rectal ulcer, through the proctoscope. Sterile cotton swabs on long applicators should be prepared and the ulcer swabbed out after the patient has used a cleansing enema. The swabs should be placed immediately in tall tubes of glucose brain-broth. If one is unable to obtain material in this manner, swabs should be taken from the pus of a freshly passed stool. After the tubes have been incubated at 37.5° C. for four to six hours, three additional tubes should be inoculated from each original tube by shaking out the swab in each tube successively, leaving it in the last one. This makes a set of serial dilutions. One set of tubes, inoculated with one swab, is now heated in a water bath for forty-five minutes, at 55° C., in order to kill Gram-negative bacilli, for it has been found that the diplococci are fairly thermostable. All the tubes are now incubated for eighteen hours, after which a Gram-stained smear is made and examined from each of the eight tubes. From this study, one or more tubes are selected on the basis of which tubes contain most Gram-positive diplococci; the others are discarded.

From these selected tubes, blood agar plates are poured by the following method: A capillary drop of brain-broth culture is mixed with 10 c.c. of physiologic solution of sodium chloride and from this mixture a capillary drop is taken and is placed in 10 c.c. of melted blood agar; then several dilutions are made from this mixture, pouring the plates and incubating over night. The colonies of diplococci will be very small and translucent, often surrounded by a green zone in which is a suggestion of slight hemolysis. Several of these colonies should be fished, transferred to brain-broth, and incubated for eighteen hours. Smears should be made from the cultures and examined; if they contain typical Gram-positive diplococci, composed of lancet-shaped organisms, the organisms may be con-

sidered the same as those described by Bargen. They can be further identified by being agglutinated by immune serum, and by observing that they ferment dextrose, lactose, maltose, saccharose, raffinose and sometimes salicin. The final test, according to Bargen, is to produce typical lesions in an experimental animal by intravenous injection.

Intestinal Tuberculosis

Although many attempts have been made to devise laboratory methods to detect the presence of tuberculous ulcerations in the bowel, but little information can as yet be obtained from such tests. Hardly had the organism been described by Koch than Lichtheim had observed that bacilli of tuberculosis could be found in the feces as frequently as in the sputum, but he held that they occurred in the stools only if patients had intestinal tuberculosis. From this time on, numerous investigators have studied the relation of pulmonary tuberculosis to the finding of bacilli in the feces. It must be borne in mind that acid-fast bacilli occur in the feces of normal individuals, and that at least some of these are similar in shape to bacilli of tuberculosis. It has been demonstrated by cultural and experimental methods that these are not Mycobacterium tuberculosis but it is frequently impossible to distinguish them from Mycobacterium tuberculosis by examination of smears.

As long ago as 1896, Biermann advanced the view that finding bacilli of tuberculosis in the feces was of no value toward establishing the diagnosis of intestinal tuberculosis, but his paper was overlooked by many who have followed, and much energy has been expended in trying to correlate the finding of bacilli in the feces with clinical findings. Philip and Porter, in 1910, after studying ninety-nine persons who had pulmonary tuberculosis, found acid-fast bacilli in the feces of 75 per cent, and in the same year Alexander found bacilli of tuberculosis in the feces of thirty-eight of forty-five cases of pulmonary disease. Engleson studied sixty cases and found bacilli in the sputum in forty-one, in the feces in forty-four, and in the rectal mucus in fifty-seven. Nüssel and others have shown that bacilli can be found in the feces in practically every case of pulmonary tuberculosis if proper methods are employed. Indeed it is claimed that one can often find Mycobacterium tuberculosis in the feces before it is found in the sputum in some cases of pulmonary tuberculosis. Not only are the bacilli swallowed but many are eliminated into the bowel with the bile.

It becomes evident, therefore, that finding bacilli of tuberculosis in the feces does little to establish the diagnosis of tuberculous enteritis. For finding such bacilli in feces it is best to concentrate the material by the Reh method, which consists of taking a piece of feces, from 1 to 2 gm. in weight, mixing it with enough water to make it half fluid, then adding ether and shaking. The ether is poured off, centrifuged, and a smear of the sediment is stained.

The gross appearance of the stool in cases of intestinal tuberculosis gives but little help, but a frank intestinal hemorrhage, if a person has tuberculosis, should make one very suspicious of ulceration in the bowel. Many workers have observed that usually, if ulceration is present, either microscopic blood or occult blood can be demonstrated. The benzidine test should be used, with a thorough understanding of the limitations of the test. The patient should be on a meat-free diet for seventy-two hours before the test. To perform the test a gram of feces should be emulsified in at least 10 c.c. of ether and the ether discarded. The feces should next be extracted with 5 to 10 c.c. of a mixture half of glacial acetic acid and half of ether, and the supernatant fluid filtered. To the filtrate is added about 50 mg. of benzidine, freshly dissolved in 1 c.c. of glacial acetic acid and immediately followed with 1 c.c. of hydrogen peroxide. If occult blood is present, even in a trace, a blue color will form within thirty seconds. This test is very delicate and if positive is highly suggestive of intestinal ulceration when the patient suffers from a tuberculous condition, provided he is not swallowing blood from the lung. Few have studied the presence of pus in feces in tuberculosis but Pritchard found it in thirty-two of his forty-five patients who had intestinal ulcerations. If pus and Mycobacterium tuberculosis are both found in a stool, and if the test for occult blood is positive, a presumptive diagnosis of tuberculous enteritis seems justified.

Food Poisoning

Few conditions encountered by general practitioners are as puzzling as sudden onsets of violent diarrhea or dysentery. Most of these go

undiagnosed as to etiology and many are of short duration. When the upset is but moderately severe, and lasts but a day or two, the common diagnosis is "something you ate"; in the light of present knowledge the diagnosis is competent. Nevertheless, more definite information is available at present. In many cases, the symptoms of gastro-enteritis are attributable to some form of food poisoning and are caused by various bacteria of which the staphylococci form a prominent group.

As a cause of food poisoning, staphylococci were first recorded in the literature by Barker, in 1914, and the evidence was critically analyzed. The cases occurred on a farm in the Philippines, and the patients had drunk the milk from a certain cow, after the milk had been kept at room temperature. The fresh milk did not cause illness. Sixteen years later Dack reported a similar outbreak in Chicago, caused by a yellow staphylococcus isolated from samples of cake. Bacteria-free filtrates, in amounts of 2 to 10 c.c., produced violent gastro-enteritis in volunteers. Since then many similar occurrences have been recorded and the organisms have been isolated from other foods: chicken gravy, devil's food layer cake, and chocolate éclairs.

The staphylococci have been yellow, and numerous volunteers have demonstrated that toxin derived from these organisms produces typical symptoms, as does the toxin when fed to rhesus monkeys.

Unfortunately it is almost impossible to make a laboratory diagnosis by examination of the patient or his feces, since living organisms may not be present; they may have been killed by heating the food. Even if living organisms are present in the feces the chances of obtaining them and proving their pathogenicity is slight. The only means of positively establishing the diagnosis is to obtain samples of the food eaten, and from them to isolate a yellow staphylococcus which produces typical toxin. In the past the toxin has been tested on volunteers, but by carefully controlling the reaction of the stomach of a guinea pig to a pH of 7.3, uniform results can be obtained on that animal. Usually several persons are affected, since foods are usually shared, and this of itself helps in the etiologic diagnosis.

A number of other bacteria have been identified with food poisoning which is evidenced by gastro-enteritis, and by violent diarrhea or dysentery, with abdominal pain. Most prominent among these bacteria are Salmonella enteritidis, Salmonella aërtrycke, and Salmonella schottmuelleri. Usually these outbreaks occur in the summer months, when the bacteria have a better chance to multiply in the foods most often involved, which are meats, including shellfish and fish. These foods may be infected in their original state, or they may be contaminated in handling, especially by carriers, or even by the deposits of rats and mice; these rodents apparently act as carriers of these bacteria.

The diagnosis is established bacteriologically by study of the food in question, of the vomitus and feces of the patient, and of the blood, spleen, liver, and intestines of those who die of the infection. As a rule, the organisms do not persist in the vomitus or feces longer than a month or six weeks, and frequently they can be obtained only at the beginning of the onset. Isolation of the organisms is performed along the same lines as will be discussed in regard to typhoid fever. All forms of these organisms do not ferment lactose, and their fermentations of other sugars are quite characteristic. However, if the paratyphoid organisms are involved, agglutination tests will be useful in identifying them.

Bacillary Dysentery

As a rule bacillary dysentery is rarely seen in the Northwest; yet it is encountered enough to be considered in any general discussion of dysentery.

Last summer, at The Mayo Clinic, as elsewhere in this region, a relatively large number of strains of dysentery bacilli were isolated from patients who had dysentery and relatively severe diarrhea. One can expect to encounter a number of different types of dysentery bacilli (Shigella paradysenteriæ) which cause this malady, such as the Flexner, His-Russell, and Sonne types. So far Shiga's organism (Shigella dysenteriæ) has not been encountered in this part of the country.

The organisms are isolated from the stool in a manner similar to that in which typhoid bacilli are isolated, with one important modification. Inoculation from the stool must be made promptly; as Colonel Craig once said, "The patient should be removed from the bedpan in order to inoculate media, preferably at the bedside." As

a matter of fact not more than thirty minutes should elapse from the passage of the stool until the inoculations are made, since the organisms apparently undergo autolysis on standing. The final determination of the exact species of dysentery bacilli is made on the basis of specific fermentation reactions and agglutination tests.

The typical stool contains pus, a great deal of mucus, is liquid, even "rice water-like," and may contain blood. Large macrophages are almost always present, and may be easily confused with amebas, for often the macrophages contain erythrocytes. Their nuclei are, of course, distinguishing, and their motion, when present, is not like that of Endamœba histolytica.

The nuclei can be demonstrated easily by making a Gram stain, or with methylene blue. Amebas do not stain well by these methods, while the macrophages stain very well.

One has a much better chance of obtaining the bacilli from a stool containing blood and mucus than from any other type of movement.

It is important to note that cultures of blood and urine are almost always negative, since the organisms very seldom invade the blood stream. However, positive agglutination tests, usually at low titer, rarely as high as 1:500, are obtained after from six to twelve days of illness and may persist for several months. The test is not considered very reliable for diagnosis.

Typhoid Fever

Although typhoid fever is not classified as a form of dysentery, in a third of the cases, during the first half of the illness, or beginning in the third week, more or less severe diarrhea may occur, with or without passage of blood. This, together with the tenesmus that is frequently present, makes it necessary to distinguish the disease from the more typical dysentery.

In this state, largely through the work of the State Board of Health, there has been a considerable reduction in the incidence of typhoid fever. In large measure this has been attributable to unremitting energy in finding carriers, in particular the food-handler carrier, and in protecting others from them. Last year, however, the number of cases reported in the state was not in line with previous years. Thus, there were 217 cases in 1930, 193 in 1931, 165 in 1932, 136 in 1933, and 153 in 1934. On the basis of the four previous years, there should have been but 109 cases in 1934 instead of 153. Perhaps this rise was attributable to the peculiarly dry summer, with its high temperatures. Incidentally the mortality for the period of five years has been 10.5 per cent.

The diagnosis of typhoid fever, from a laboratory standpoint, is most satisfactory. In the first week one should expect to obtain positive blood cultures in almost every case. The earlier the culture is taken, the more likely the chance of obtaining the organism. Blood should be poured, with agar, into Petri dishes, in varying dilutions, and should be incubated for forty-eight hours if still negative at the end of twenty-four hours. Usually the colonies appear slowly, and more cultures are positive after thirty-six hours than before. If the organisms are Gram-negative, and especially if they are motile, they should be tested in sugar fermentation tubes and their identity verified, if necessary, by specific agglutination tests. After the first week the incidence of positive cultures falls, and in the fourth week it is not more than 15 or 20 per cent.

Evidence based on the Widal test can be obtained beginning with the third day, when in about 15 per cent of cases the test is weakly positive. During the second week more than 80 per cent of patients give positive agglutination tests in a titer as high as 1:100. An important feature in diagnosing typhoid fever is the increasing titer of agglutination during the illness. In these days, when typhoid vaccine is used so frequently, a Widal test is not so diagnostic as it formerly was, and it is often necessary to repeat the test and to demonstrate a rising titer before its significance can be determined.

With the appearance of an adequate agglutination titer the rose spots are seen, and from them the organism can be isolated, although rarely is it indicated, from a diagnostic standpoint, to attempt to isolate the organisms from these spots.

The organism can be isolated from the stool or urine in about half the cases during the first two weeks, but more frequently during the third, when the ulcers begin to break down. I have found that the most satisfactory method is to inoculate 1 c.c. of physiologic saline solution with a loopful of feces, and to incubate the mixture for thirty minutes. From the top layer a loopful is spread out on an Endo plate, and this is incubated in the dark for twenty-four hours.

Suspicious white colonies are fished and grown for eight hours in a tube of sugar-free broth, and from this sugar fermentation tubes are inoculated. The characteristic reactions are read at the end of twenty-four hours, and the cultures also can be tested with specific serums, for agglutinations. Urine is treated in a similar manner, except that no dilution in saline solution is necessary, and no preliminary incubation is done.

It is easier to isolate the organism from duodenal content than from the stool and it should be remarked that it is not a simple matter to obtain the organism from the stool or urine. This requires experience and skill, and attempts are frequently unsuccessful.

The methods suggested for the detection of typhoid fever by laboratory methods are equally applicable to the paratyphoid fevers.

Amebic Dysentery

Although it has been claimed that many animal parasites cause diarrhea and dysentery, not all agree that this is true. It is plainly evident, however, that Balantidium coli and Endamœba histolytica are causes of dysentery. The former parasite is rarely encountered but once observed is never to be forgotten. It is a large, oval ciliate, about 150 microns in length, and is readily seen, rapidly moving, with the low powers of the microscope. The stools passed by the patient are variable, but at times may contain blood and mucus.

Diagnosis of Endamœba histolytica, on the other hand, gives the greatest difficulties, owing to the fact that at least four other amebas may be confused with it. The minuteness of its distinguishing characteristics, and the variability in the various species of intestinal amebas, require that one shall be properly trained and experienced before attempting identification of these forms.

In acute cases of amebic dysentery the typical stool will contain dark brown streaks of mucus and the whole stool, which is small in volume, will be of dark brick color or reddish brown, owing to the presence of partly decomposed blood. Sometimes flecks of bloody mucus are present, and in these flecks amebas are most numerous. Charcot-Leyden crystals are usually present but are not diagnostic. In amebic stools, as a rule, there is more blood than pus, and when the reverse is true one should think of tuberculosis or of chronic ulcerative colitis.

In cases of amebic dysentery the amebas will be in the motile or vegetative stage, and the diagnosis will have to be made on the basis of trophozoites. Between attacks the stool may be normal, and unless a cathartic is administered the diagnosis will have to be made on the finding of cysts. A single stool from each patient, following his taking of an ounce (30 c.c.) of magnesium sulphate, will, in competent hands, disclose about 80 per cent of the infections, while one formed stool from each person will reveal only about 30 per cent of the infections. Three liquid stools may be expected to yield as large a number of positive results as six to ten formed stools. The stool should be examined as soon after its passage as possible, and if it is liquid it must be kept warm until examination. It is best to have the stool passed in the laboratory quarters. It may be necessary to examine many different portions of the stool and one should make coverglass preparations from portions which contain mucus, or blood, or both. The search should be conducted with low power ($\times$ 100) lenses—identification, with greater magnification.

It will not be practicable here to discuss the various differential features of Endamœba histolytica, and for these one must consult published monographs and texts which will not only give the morphologic details but methods of staining as well. One often has to resort to permanent fixed and stained slides before identification can be made. It is important to keep in mind the fact that the details of the nucleus are, after all, the real basis of identification, although in properly prepared fresh preparations the directional nature of the locomotion of the ameba, and the presence of ingested erythrocytes, are important features.

Sometimes one can save time by making the smear from the bloody mucus taken from an ulcer, with a wire curet, in the course of the proctoscopic examination. This material is placed on a slide, a coverglass is applied, and examination is made directly. From an amebic ulcer the organisms may be obtained in large numbers in this manner and such amebas can, without much danger of error, be called Endamœba histolytica.

During the past decade many cultural methods

for diagnosing amebic dysentery have been advanced. There is no doubt but that one may succeed in growing Endamœba histolytica on a variety of mediums. However, not all stools containing the parasite will yield positive cultures, and once the parasite is growing, the same problems of identification will arise, as well as some added confusing items. In cultures, the nuclear characteristics are modified, and until someone records these in a clear-cut manner there will remain some confusion on the subject. It is evident to anyone who has given consideration to the comparison of smears and of cultures that the skill and persistence of the microscopist will greatly determine how many more cultures than smears are found positive.

Craig's complement fixation test for amebiasis has not yet been simplified to such a degree that it can be used as a routine diagnostic method. The antigen is especially difficult to prepare and the spread between the antigenic titer and the anticomplementary titer is not great enough to avoid false positives when the test is made sensitive enough to be diagnostic.

It becomes evident that the diagnosis of amebiasis should be made only by those specially qualified, and that one should be prepared to use the method of direct smears of fresh material, the staining method on wet fixed slides, and also cultural methods.

Summary

It is clear that the laboratory investigation of dysenteric cases involves many different and highly specialized procedures as well as thorough knowledge of the course of different diseases in which dysentery is one of the symptoms. The laboratory man can be of great assistance in diagnosis and in following the course of the disease, as well as in the treatment of patients suffering from this symptom-complex. It is hoped that the foregoing discussion will serve as an outline for laboratory procedure and that it may stimulate physicians to investigate more carefully the etiologic agent involved in the cause of dysentery when that symptom is manifested by a patient.

ROENTGENOLOGIC MANIFESTATIONS OF DISEASES WHICH HAVE DYSENTERY AS A PROMINENT SYMPTOM*

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BEFORE considering the roentgenologic manifestations of the specific pathologic processes in which dysentery is a prominent symptom, I propose to remark briefly about the nature of the roentgenologic examination and what might be expected of it, especially as it is applied to the investigation of the gastro-intestinal tract. Its primary purpose is to prove the presence or absence of organic disease in those divisions of this system which cannot be visualized directly or by endoscopy. The positive contributions it makes to the diagnosis of functional gastro-intestinal disorders are of highly questionable, if not of entirely negligible, value and afford at best objective evidence of disturbances in gastro-intestinal motility which already is apparent subjectively. But in the diagnosis of organic disease of the gastro-intestinal tract, the efficiency of the roentgenologic examination is proved. It can be made, and in the hands of competent examiners actually is made, to disclose organic disease whenever present. Moreover, it can be depended on to supply desired information about the pathologic nature, extent, severity, and important anatomic complications of the lesion which it has been instrumental in disclosing. In precision and reliability it approaches that of direct inspection at necropsy or exploratory operation.

To the experienced physician the term "dysentery" suggests at once a disorder or dysfunction of the large intestine or terminal portion of the small intestine, because in the vast majority of instances in which an organic lesion manifests itself by dysenteric symptoms, that lesion will be found in the colon or in that portion of the small intestine just proximal to it.

*From the section on Roentgenology, The Mayo Clinic, Rochester, Minnesota. Part of symposium read at the annual meeting of the Minnesota State Medical Association, Minneapolis, June 25, 1935.

The group of diseases of the large intestine in which chronic dysentery is the most prominent symptom is the chronic ulcerative colitis group. The term "chronic ulcerative colitis" is used here in a general rather than in a specific sense. Only three etiologic types are commonly encountered: the streptococcic type, the tuberculous type, and the amebic type. Others, in my experience at least, occur rarely, and are readily recognized as entities. It has not been found practical to consider them seriously before the three prevalent types, which have just been mentioned, have definitely been excluded in the diagnosis.

All types of organic colitis have similar gross pathologic appearances. General contraction of the affected portion of intestine—which implies narrowing, shortening and mural thickening and mucosal destruction are common to all types. With the exception of the changes in the mucosal surface of the intestine, none of these macroscopic features are in themselves pathognomonic, since the pathologic processes of which they are a part are essentially the same, whatever the etiology of the disease. The mucosal lesions are, however, more or less distinctive macroscopically; hence, direct inspection of the mocosal surface of the bowel, as for instance by endoscopy, usually, but not invariably, will reveal the etiologic nature of the pathologic process.

The fundamental principle that roentgenologic manifestations reflect the anatomic changes produced by, or associated with, the underlying pathologic changes holds eminently true in the roentgenologic diagnosis of this group of diseases; it is most important, however, to realize that the ulcerative aspect, which is the pathognomonic feature at direct inspection, is of minor significance in the roentgenologic diagnosis. Narrowing and shortening of the bowel are easily recognized roentgenologically; mural thickening and diminished mobility and flexibility are signs elicited by the reaction of the affected intestinal segment to the pressure of the roentgenoscopically controlled palpating hand, and destruction of the mucosa is revealed by significant changes in its relief. These constitute the roentgenologic syndrome of ulcerative colitis in general (Fig. 1). By themselves, however, they are not peculiar to any particular type of ulcerative colitis. The differential diagnosis is based on an entirely different group of roentgenologically demonstrable features. Among the most important are the site of apparent earliest and most severe involvement, the distribution of the disease in the bowel, the direction of its extension, the intensity of the process, and the related roentgenologic findings in other organs.

Streptococcic ulcerative colitis is widely known as "chronic ulcerative colitis," a term which is considered inadequate because it is not sufficiently specific. It is the disease with which Bargen's bacteriologic researches have chiefly been concerned. In this type of ulcerative colitis the rectum is usually the site of early and most severe involvement, and since the proctoscopic examination provides a pathognomonic picture, the diagnosis should be made by this method, although when the involvement is sufficiently extensive the roentgenologic syndrome is but little less characteristic and specific. The principal function of the roentgenologic examination is the determination of the extent of the pathologic process, the presence or absence of the various complications of the disease, and, in those comparatively rare instances in which the disease has not primarily involved the rectum, it offers the only nonsurgical objective evidence of the pathologic process.

The general roentgenologic picture of the disease is fairly uniform. The affected portion of the bowel is narrowed and shortened, the walls are thickened, the contours are smooth and straight, and mucosal destruction of some degree is present. These changes are more intensified in the streptococcic type than they are in the other forms of ulcerative colitis. The most severe involvement is seen in the rectum and in the sigmoid flexure of the colon; progression is proximal, and the intensity of the changes diminishes gradually from below upward. This roentgenologic appearance is so regular and so characteristic in almost all instances of the disease that it practically never is justifiably confounded with that of any other known disease of the intestine.

The roentgenologic manifestations of the tuberculous and amebic types of ulcerative colitis differ from those of the streptococcic type principally in that the earliest and most severe involvement is found to be in the most proximal segments of the colon, and the changes in these

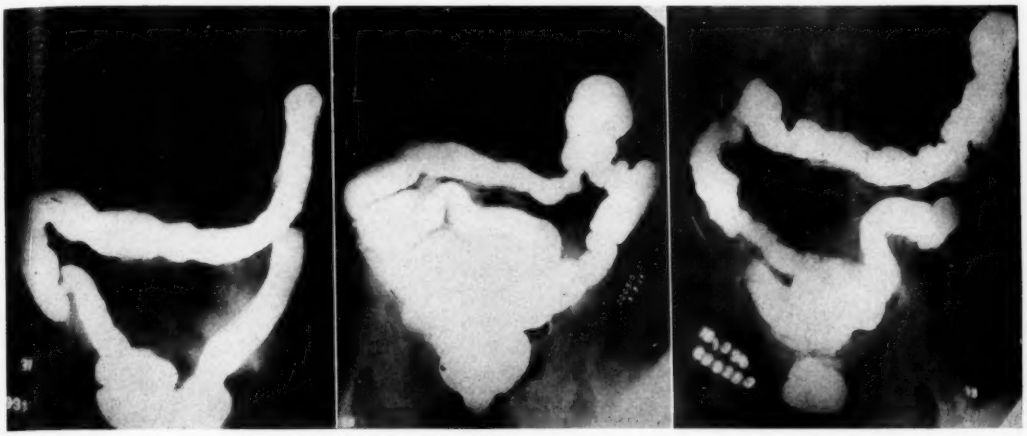

Fig. 1. The three most commonly encountered types of ulcerative colitis. Streptococcic (left), tuberculous (center), endamebic (right). All have narrowing, shortening, suppression of haustral markings in common. The colon in all of these instances has been distended with the opaque enema.

types progress distally as well as proximally. This progression takes place by the development of multiple discrete ulcers which eventually coalesce. The fecal current assists in the spreading of the disease by carrying infectious material from ulcerated surfaces to other vulnerable regions of the intestine. Thus, the extension is unlike that of the streptococcic type, in which the disease spreads against the fecal current in a creeping, step by step fashion, and results in a diffuse symmetrical involvement of the entire circumference of the bowel. In tuberculous and amebic ulcerative colitis the tendency is toward an irregular involvement of the circumference, and toward an interrupted rather than a continuous extension along the longitudinal axis of the intestine.

Ulcerative tuberculous enterocolitis is practically always secondary to some distant active focus of tuberculosis, usually in the lungs, and from foreknowledge of the existence of such a focus the diagnosis of an intestinal lesion might be inferred, no matter what intestinal abnormality is discovered or assumed to be present. This inference does not merit implicit reliance, however, since non-tuberculous intestinal lesions may and do coexist with extra-intestinal tuberculous foci, and tuberculous intestinal processes are not frequently encountered in cases in which no other tuberculous focus is demonstrable. Careful study of the anatomic changes as they are mirrored in the roentgenologic picture of the involved segment of intestine is a much more intelligent approach to the diagnosis, and it is reasonable to assume that these anatomic changes will be apparent roentgenologically as early as they manifest themselves clinically by functional abnormalities and subjective symptoms. Typically tuberculous intestinal lesions are distributed most densely in the terminal portions of ileum, in the cecum, and in the proximal portion of the colon, and it is this characteristic distribution which constitutes the important roentgenologic evidence of intestinal tuberculosis.

Amebic ulcerative colitis, too, is a disease primarily of the proximal portion of the colon and of the cecum. Amebic lesions in the terminal portion of the ileum are but rarely found, even in the final stages of the disease. As is the case in the streptococcic type of ulcerative colitis, the roentgenologic examination does not reveal the primary diagnosis. The presence of Endamœba histolytica in the stools means, according to Craig and others, that intestinal ulceration of some degree has taken place. In most instances of endamebic parasitism seen in this latitude, extensive intestinal ulceration is by no means the rule, and in my experience hardly more than 50 per cent of known carriers of Endamœba histolytica have intestinal lesions severe or extensive enough at the time of examination to be demonstrable roentgenologically. It is to be noted in this connection that the intensity of the anatomic changes and the intensity of the intestinal symptoms of amebiasis do not go hand in hand.

When roentgenologically demonstrable patho-

logic changes in the intestine do occur in cases of amebic parasitism, they are essentially the same as those produced in association with the other types of ulcerative colitis except that the process seems to be one of comparatively diminished intensity and severity. Amebic ulcerative colitis has a fairly distinctive roentgenologic "look," difficult to describe, but the most significant roentgenologic finding is that of an ulcerative colitis more or less diffusely spread over the cecum and the immediately adjacent ascending colon, without recognizable ileal involvement. If the process has a more general colonic distribution, the more dependent segments of the colon are sites of predilection, and these are responsible for the patchy, irregular deformity. Often relatively unaffected loops of colon are seen interposed between others which are definitely diseased.

To obviate as much confusion as possible the attempt is made here to consider only the typical and most commonly encountered manifestations of this group of diseases. It is true, of course, that atypical manifestations occur to confound even the most experienced observer, but such instances fortunately are rare; and it is somewhat consoling to the roentgenologist to note in such instances that other interested parties, not including the patient, of course, are frequently quite as much at sea.

Patients afflicted with the so-called infectious dysenteries, bacillary dysentery and typhoid fever, are rarely referred for roentgenologic examination, presumably because of the acute and fulminating character of the clinical manifestations. Chronic forms of bacillary dysentery are either of extremely low incidence, or their roentgenologic manifestations are as yet indistinguishable from those of ulcerative colitis, which have just been considered.

Occasional instances of chronic ulcerative enteritis and enterocolitis occur, in which involvement is confined to regions of the small and large intestine. Frequently they make themselves manifest clinically by dysenteric symptoms. Pathologically, the involved segment is affected in very much the same manner as is the colon in one of the types of ulcerative colitis. It is to be expected that the roentgenologic manifestations will also be similar, depending entirely as they do on the character, severity, and extent of the pathologic changes. Significant again is the mural thickening and narrowing of the lumen, shortening, pronounced stiffening, and diminished mobility of the involved segment, with greater and lesser degrees of mucosal destruction (Fig. 2). All of these changes are readily revealed by the properly executed roentgenologic examination of the small intestine. Such examination demands closest scrutiny of each individual portion of the small intestine by multiple roentgenoscopic observations of the opaque meal as it winds its way through the complicated system of small intestinal coils. Combined with this is the special roentgenologic examination of the terminal 25 to 100 or more centimeters of ileum after it has been distended by reflux of the opaque enema through the ileocecal orifice (Fig. 3). This procedure is to be looked on as an integral part of the basic examination of the colon with the opaque enema, in much the same manner as the examination of the duodenum is an integral part of the examination of the stomach. The roentgenologic examination of the small intestine is difficult only because it is comparatively tedious, but it can be made quite as efficient as the roentgenologic examination of the more proximal and more distal divisions of the alimentary tract.

Pathologically allied to all of these organic intestinal disorders, but only rarely causing dysentery, are the specific and nonspecific granulomas. Granulomas are called specific if a primary etiologic factor, such as the Bacillus of tuberculosis, Endamœba histolytica, or Actinomyces can be shown to be operative in producing the lesion; they are called nonspecific, if no such factor is recognized. Since they are almost identical in their gross morphology, they have very similar roentgenologic features. They are essentially inflammatory tumors, and, as such, the important diagnostic problem is to recognize them as non-neoplastic in character. This is efficiently accomplished at the roentgenologic examination, principally because neoplastic lesions of the intestinal tract manifest themselves by such distinctive and pathognomonic roentgenologic signs that the diagnosis of "granuloma" is put forth when these signs fail to be exhibited. Roentgenologically, however, it is rarely possible to qualify the diagnosis of granuloma by giving it an etiologic name. Guesses at the etiology of these lesions are sometimes hazarded, but the roentgenologist usually offers the diagnosis of

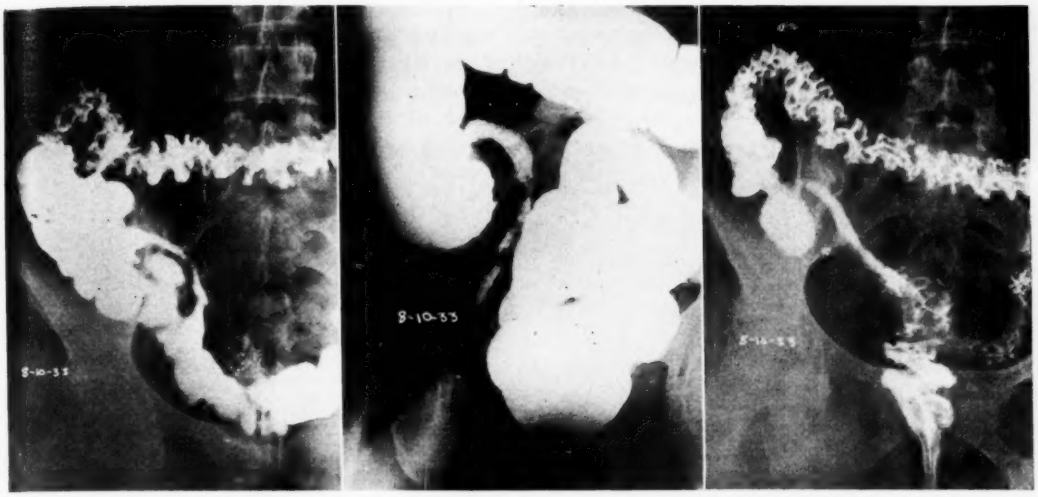

Fig. 2. Diffuse ileitis in which only the terminal segments of the ileum are involved. The opaque meal (left) six hours after ingestion, showing the narrowing of the involved ileum. The colon and terminal ileum of the same patient are shown distended with the opaque enema (center) and after evacuation of the opaque enema (right). The roentgenologic findings of this disease described in the text are best elicited by this method.

granuloma without further qualification, and is content if he is satisfied that the lesion is not malignant.

Of the neoplastic lesions which have dysentery as a prominent symptom, only the conditions known as polyposis and polypoidosis need be taken into consideration. By the term "polyposis" is meant that condition in which the mucosal surface of the bowel or a relatively large portion of it is regularly or irregularly studded with numerous, sometimes innumerable, small sessile or pedunculated, discrete polypoid or bud-like adenomatous tumors. Polyposis is called primary when there has been no antecedent ulcerative condition predisposing to or provoking adenomatous hyperplasia. The tumors are therefore true neoplasms. Conversely, when such an ulcerative process has existed, the condition is designated as secondary, and the lesions are looked on as regenerative or reparative phenomena. Both have a decided tendency toward malignant transformation. By the term "polypoidosis" is meant that condition in which the entire mucosal lining of the bowel, or a large part of it, seems to have been transformed into a convoluted, luxuriant mass of adenomatous tissue. It is always primary, and according to Broders is essentially a benign process, except that discrete sessile or pedunculated adenomas, which are almost always found distributed densely or sparsely in the transformed mucosal surface, may be or may become carcinomas. Hence, for practical purposes, the distinction between the two words is relatively unimportant from a clinical standpoint.

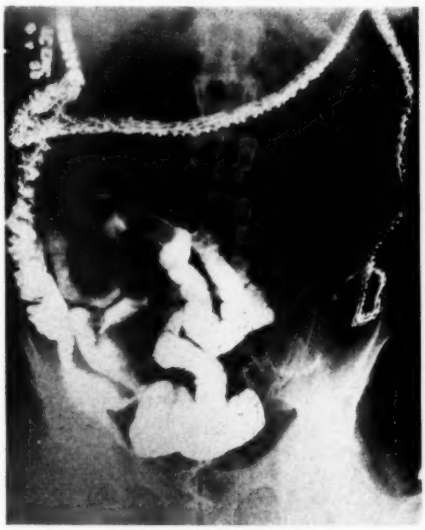

Fig. 3. The colon and ileum after evacuation of the opaque enema. The ileum has been filled with the opaque suspension by reflux through the ileocecal valve.

Roentgenologically, these conditions of the large intestine are of extreme interest because they produce no readily recognizable deformity of the shadow of the lumen of the bowel, and it

was not until Fischer described his so-called "double contrast technic" that the roentgenologic diagnosis was made with any great degree of confidence. True, if the individual polypoid lesions were large, they produced the smooth ovoid or rounded central filling defects in the barium column, but the lesions are not often of sufficient size to do this. With the double contrast method, however, a very vivid and pathognomonic representation of all types of polyposis, polypoidosis, and single polypoid lesions is obtained, and it is possible to visualize even the smallest mucosal excrescences (Fig. 4). The small polypoid lesions of polyposis are seen as bud-like projections into the colonic lumen, or as circular rarefied defects on the mucosal surface corresponding to the site where the pedicle of the polyp is attached. In the primary type of polyposis, evidence of antecedent disease is lacking and the mucosa between the discrete, fairly regularly distributed polypoid lesions is intact. In the secondary type, the pathologic changes produced by the primary disease are manifest, and the tag-like sessile and pedunculated masses are clearly visualized and are irregularly strewn over the internal glazed surface of the bowel. The "double contrast" roentgenogram of polypoidosis is especially vivid. The opaque material settles

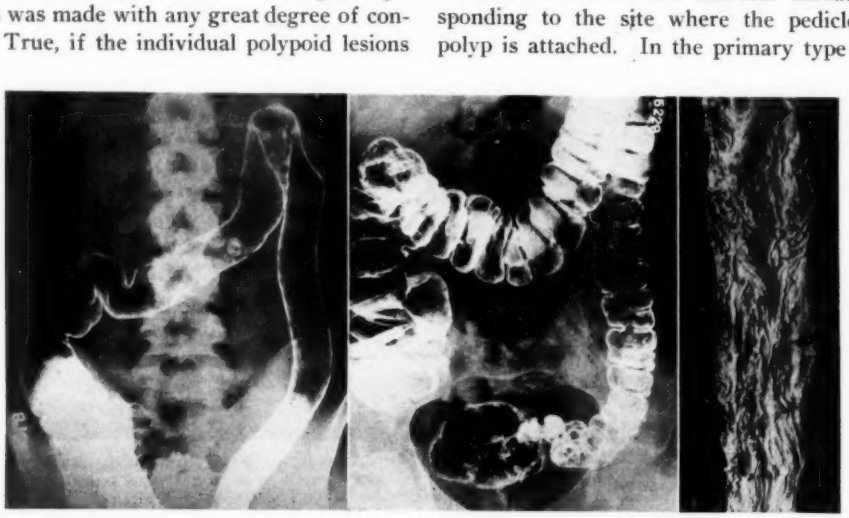

Fig. 4. Solitary secondary polypoid lesion in transverse colon (left). The patient has chronic ulcerative colitis. Double contrast roentgenogram showing diffuse primary polyposis (center). The small round rarefied areas are the sites of the small polypoid lesions, the morphology of which may be noted from the necropsy specimen (right).

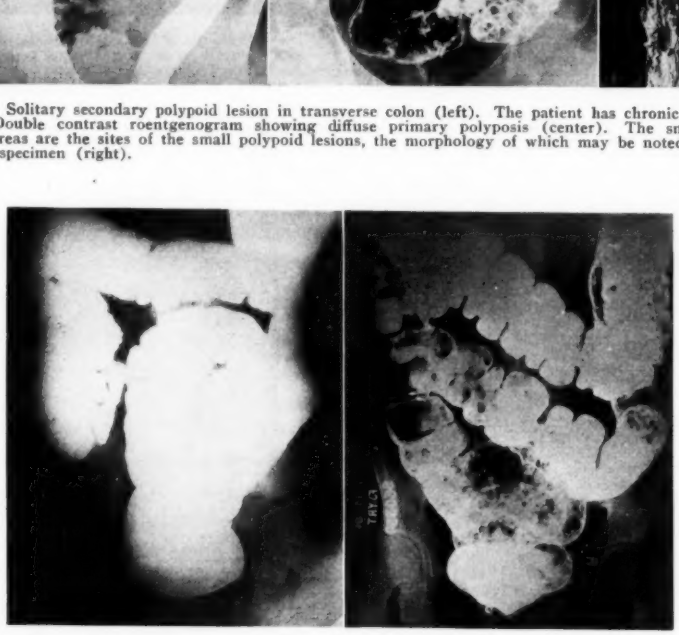

Fig. 5. Diffuse polypoidosis. Opaque enema (left) which fails to reveal the lesions. Double contrast method (right) which shows the pathognomonic picture of the disease.

into the crevices of the villous adenomatous tissue, and when the lumen is redistended with air or inert gas, a pathognomonic lacy internal relief pattern is developed. This produces, without doubt, one of the most striking pictures the field of roentgenology has to offer (Fig. 5).

It may be stated as a principle that it is rarely, if ever, possible to elicit roentgenologic signs by which one can affirm that a given neoplastic lesion is benign. In the gastro-intestinal tract there are no positive roentgenologic signs of malignancy. Hence, in connection with these polypoid lesions it is important to bear in mind that the roentgenologic examination may reveal that a given lesion lacks the macroscopic characteristics pathognomonic of malignancy. Microscopic examination may reveal, however, that any one of these grossly benign lesions is actually malignant.

Very severe diarrhea without intestinal bleeding is a prominent symptom of a group of diseases which for convenience are designated as deficiency diseases, and of which chronic idiopathic steatorrhea, tropical and nontropical sprue, and pellagra are the most frequently encountered examples. Striking roentgenologic findings have been described; these correspond to anatomic dilatation, edema, atrophy, and congestion of various portions of the small and large intestine, especially of the former. The contours of involved segments are either abnormally smooth or abnormally shaggy, and the normally prominent pattern of the mucosal relief is markedly exaggerated or markedly suppressed. The opaque material is sometimes gathered in pools in isolated dilated segments. The motility is usually considerably subdued. The picture is rather typical and common to all of the conditions under consideration, but it is difficult to describe. Rather striking is the return of the intestine to normal with regression of symptoms.

It is true that in one phase or another of its clinical course almost any organic disease of the intestinal tract may be associated with dysenteric symptoms. Here, however, only those organic diseases in which dysentery is a more striking feature, have been given attention. Dysentery is not a prominent symptom of carcinoma, but the possibility that malignancy, especially of the lower colonic segment, may be manifested by dysenteric symptoms must be kept in mind. Of course, any significant change in intestinal habit, be it constipation or diarrhea, which does not tend to disappear within reasonable limits of time, may be the signal of serious organic disorder, and the roentgenologic examination, reaching as it does to a solid foundation in normal and pathologic anatomy for its diagnostic data, has become such an important part of the complete health audit, that the title of "autopsia in vivo," can well be applied to it.

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DYSENTERY: ITS MEDICAL MANAGEMENT*

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FROM the standpoint of the average practitioner of medicine, it is safe to say that intestinal disorders associated with dysentery are the cause of more distressing problems than disease of almost any other part of the body.

In general, dysentery may be divided into that attributable to organic causes and that attributable to functional disorders. Organic intestinal disorders readily divide themselves into neoplastic and non-neoplastic diseases. The latter class might better be designated as diseases of inflammatory origin and those of which the origin is some deficiency. Functional intestinal disorders readily divide themselves into local, systemic, and metabolic (Table I).

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The most important differential diagnostic method of studying cases of dysentery is by careful and detailed taking of histories. However, to rely on the history alone will result in many regrettable errors of omission. Many physicians will recall cases of irritable colon in which, for months, treatment was for colitis, or they may recall what was more serious, cases of carcinoma, in which the mistaken diagnosis of colitis was adhered to until chance of cure had faded. Therefore, while taking of the history is the indispensable and most important guide to the diagnosis, there is no other series of similar symptom-provoking conditions that lends itself so well to further routine study as the dysenteries. A well-ordered set of objective investigations will lead to the correct diagnosis in nearly all cases of dysentery.

Symptoms

The nature, type, and severity of diarrhea is of utmost differential diagnostic importance. Whether a patient has twenty loose, watery stools, or three or four mucopurulent rectal discharges in each period of twenty-four hours is diagnostic. The amount of tenesmus, straining at stool, incontinence, abdominal cramps, borborygmus, and abdominal distention are all very important. The presence or absence of mucus in the stool has no diagnostic significance. Mucus is the normal colonic secretion. On the other hand, the presence or absence of blood in the stools is the most important sign, distinguishing organic from functional disease. Yet, the absence of blood does not rule out organic disease. It is well to consider that all rectal bleeding is attributable to carcinoma until proof to the contrary is available. The quantity of pus in the stools or rectal discharges has great significance. Emaciation, rapid loss of weight, and anemia have great diagnostic value.

General Physical Examination

General inspection of the patient is important. The facies are often suggestive of the type of disease. Pallor and anxiety occur with severe organic disease or, on the other hand, full robust features may be noted in cases of functional disorder. Examination of the chest may elicit the findings of tuberculosis. The scaphoid abdomen may suggest tuberculosis or chronic ulcerative colitis. The cordlike feeling imparted by the colon may be suggestive, if on the left side, of chronic ulcerative colitis, if on the right, of other inflammatory disease. Finally, the most important part of the physical examination is careful, digital exploration of the rectum. The wall of the rectum in all functional disorders is soft and pliable and the mucosa is smooth and velvety. The wall of the rectum in amebiasis and tuberculosis may also be soft and pliable but if lesions have advanced to involve the rectum, irregular depressions will be found in the mucosa. The wall of the rectum in chronic ulcerative colitis will be stiff, thickened, the lumen narrowed, and the mucosa will appear roughly granular. Polyps in the rectum are readily palpable and carcinoma imparts a characteristic feeling to the finger.

TABLE I. CONDITIONS ASSOCIATED WITH DYSENTERIC SYMPTOMS

I. *Functional* intestinal disorders
  1. Local
    a. Irritable or unstable colon: "Mucous colitis"
    b. Gastrogenic diarrhea
    c. Foreign bodies
  2. Systemic
    a. Nervous diarrhea
    b. Allergic diarrhea
    c. Food poisoning
    d. Trichinosis
  3. Metabolic
    a. Hyperthyroidism, uremia, and so forth
II. *Organic* intestinal disorders
  1. Neoplastic
    a. Polyposis and polypoidosis
    b. Carcinoma
    c. Sarcoma: Lymphosarcoma
  2. Non-neoplastic
    a. The *ulcerative colitis* group
      1. Streptococcic
      2. Tuberculous
      3. Amebic
      4. Unknown etiology (?)
    b. The *infectious dysentery* group
      1. Bacillary dysentery
      2. Typhoid fever
    c. Granulomatous processes
      1. Specific: Tuberculomas, amebic granulomas, and so forth
      2. Nonspecific
    d. Regional enteritis, colitis, and enterocolitis
    e. Deficiency diseases
      1. Pellagra
      2. Sprue

Stools and Rectal Discharge

Doctor Magath has thoroughly covered this part of the subject, but let me speak, again, of the immense value of gross inspection of the

stools. During some stages of chronic ulcerative colitis, the characteristic sanguinopurulent rectal discharges alone allow the diagnosis to be made.

Proctoscopic Examination

Many organic lesions of the colon can be positively diagnosed by visualization through the proctoscope or sigmoidoscope. Thus, the uncomplicated pictures of chronic ulcerative colitis, tuberculosis, and amebiasis are characteristic. Proctoscopic examination of the rectums of patients who have polyps or carcinoma offers the added advantage of allowing removal of specimens. Frequently the diagnosis of diverticulitis can be made through the proctoscope by visualization of the upper rectal sacculation and spasm. Proctoscopic examination is of great importance in functional colonic disorders, because it discloses the fact that the lining of the bowel is normal.

Roentgenologic Examination

This should always be the final one of the series of investigations of the bowel. Doctor Weber has discussed this in detail and I wish only to emphasize the place of this examination, that is, as the last step of a complete and thorough intestinal study.

Order of Examinations

To recapitulate, the order of examination of a patient who has dysentery, providing the patient's condition warrants, should be as follows: thorough physical examination, digital examination of the rectum, examination of stools, proctoscopic examination and roentgenologic examinations.

Other procedures may be advisable, such as analysis of gastric content, investigations of allergy, and food elimination tests, but these will be found advisable in a relatively small number of cases and usually need be made only when the other tests have not yielded sufficient diagnostic data.

Careful studies of the blood can be made while the other tests are being carried out and should be done routinely.

Treatment

A detailed discussion of the management of any one of the conditions listed in Table I cannot be given here. Furthermore, the duty of the clinician is largely concerned only with the diagnosis of many of these conditions. However, there is no group of human ailments which demand closer coöperation of the surgeon, clinician, roentgenologist, and the laboratory physician than the many disorders of the intestine. Hence, there is no real division of responsibility in the care of these patients, but rather, the whole group is best handled by the combined and coöperative efforts of all concerned. My remarks concerning the therapeutic efforts made for this group of patients will be limited largely to three diseases: amebiasis, chronic ulcerative colitis, and functional intestinal disorders.

Amebiasis.—Chemotherapy plays a very important rôle in the treatment of amebic dysentery. The purpose of therapy in these cases is three-fold: to eradicate the parasites in the intestinal lumen, to eradicate the parasites in the walls of the intestine and other distant foci, and to promote healing of the lesions they have produced.

The following combinations of drugs have been found to produce these results in a very satisfactory manner. For the average case, emetine hydrochloride grain ⅔ (0.043 gm.) twice a day is administered hypodermically until 4 grains (0.24 gm.) have been given. For the more acute cases 1 grain (0.065 gm.) twice a day up to 6 grains (0.4 gm.) may be advisable. At the same time, tablets of treparsol, each 0.25 gm. are administered. One tablet is chewed before each of twelve successive meals (three times a day), the course taking four days. A rest of a week follows, and the same course of treatment is repeated. Two courses of emetine are usually sufficient, nor is it often safe to give more. Three courses of treparsol are usually required. Between the second and third courses of treparsol, and after the third, one of the compounds of iodine such as vioform may be given. Tablets of this are of the same size as those of treparsol.

Diet should be generous but bland and will be graded, more bland or less bland, according to the severity of the disease.

After completion of the course of treatment, stools should be examined by a competent parasitologist, and such examination should be repeated several months later.

Chronic ulcerative colitis.—This is one of the most serious diseases to attack the digestive tract

of man. At present, there are fairly well standardized methods of management of this disease. Much, however, remains to be done for control of this disease and its many complications. Uncomplicated cases of chronic ulcerative colitis are medical problems. Some complications of the disease are surgical, and certain operations may become essential adjuncts to well managed medical cases. The surgical indications will be discussed by Doctor Dixon.

No single therapeutic agent will suffice in the care of these patients. Present management in use at The Mayo Clinic divides itself into the following departments: (1) rest and restful recreation, (2) a careful dietary program, (3) administration of serums and vaccine, (4) removal of foci of infection, (5) transfusions of blood, (6) supportive measures, (7) careful nursing, (8) physiotherapy, hydrotherapy, and occupational therapy, (9) administration of drugs, and (10) local treatments.

Chronic ulcerative colitis should be looked on much as is tuberculosis, and so a well-ordered, graduated program of rest, at first rest in bed, then graded activity, and finally mild physical recreation, are in order.

Many patients who have had this disease have, in the course of time, omitted one food and then another from their diet so that ultimately their diet has become very limited. It is well then to return them by easy stages to a generous, high calorie, high protein type of diet, beginning with easily assimilated, palatable, non-irritating foods and increasing the diet day by day as rapidly as the patient's condition will tolerate. Not infrequently, parenteral feedings in the form of intravenously administered solutions of glucose or subcutaneously administered physiologic solution of sodium chloride, to restore an adequate fluid balance, are indicated.

The serum prepared by immunizing horses against the diplostreptococcus of colitis may be administered intramuscularly, or, in some severe cases, intravenously. Results with the use of this serum are most gratifying. The anti-colon bacillus serum recently prepared by Schwartzman bids fair to have value. The reactions from antidysentery bacillus serum are frequently so severe that their use is indicated only in the most resistant cases. Their value, as anything more than a nonspecific foreign substance, is problematical. Vaccines prepared from the diplostreptococcus isolated from the rectal ulcers should be administered subcutaneously in the less severe cases, or when active and severe symptoms have subsided.

Distant foci of infection, particularly about the mouth, such as tonsils and abscessed teeth, should be removed.

Blood transfusions have value in two phases of the disease; when the individual is greatly depleted or when the individual has had a long siege of fever and sepsis, and is anemic. A series of small transfusions, say, about 250 c.c. of blood each, given every four or five days, for four or five weeks, have much greater value than one or two transfusions of larger amounts.

Osler has well said that disease above the diaphragm makes for optimism and that below the diaphragm for pessimism. Hence, in this disease, any measures which will make for physical stimulation and distraction are in order. For this reason, mild forms of occupational therapy have great value.

Many drugs have been advocated in the treatment of chronic ulcerative colitis. No single one has helped more than a few individuals. Sedatives, and particularly codeine and other forms of opium, are decidedly indicated in the more severe cases. Tincture of iodine, given by mouth, has value in selected cases. Arsenic, in the form of stovarsol, treparsol, or carbarsone, is dangerous when used for treatment of chronic ulcerative colitis. It has been used somewhat promiscuously recently, particularly since the recent outbreak of amebiasis. It frequently has seemed to be the basis of severe flare-ups. Its only indication is as a tonic in very small amounts after the patient has ceased passing blood. A warning should also be expressed about the use of mercury, in such forms as mercurochrome.

Local treatments are indicated only when there is much anal discomfort, as from fissures and fistulas, or when the lesions are confined to the most distal segments of the large intestine. Chronic ulcerative colitis is a disease not of the mucosa but of the intestinal wall, and hence colonic irrigations not only fall entirely short of the purpose for which they are intended but often cause irreparable irritation.

From these remarks, it becomes obvious that a well ordered program of activities is necessary for adequate treatment of patients with chronic ulcerative colitis.

Irritable colon, unstable colon, "mucous colitis."—The most common intestinal dysfunction to come under the care of the practitioner of medicine falls in this category. Yet the diagnosis never should be made until every possible chance of organic disease has been excluded. Therefore, the most important therapeutic measure in these cases is careful taking of histories and extremely careful and detailed objective investigations. One must be able to assure the patients, without a shadow of doubt, that they do not have serious colitis or carcinoma. Most of the problems are individual and really should not be classed under the heading of dysentery; yet so often are they confused with real intestinal disease that these few comments may not be amiss. Among the measures particularly required for individuals afflicted with such unstable colons are careful study of their mental reactions, ample rest and diversion, freedom from nervous tension, careful regulation of diet, and advice about mild and soothing sedatives. The question of allergy must be carefully investigated. If achlorhydria is present, dilute hydrochloric acid should be tried. Finally, the question of deficiency disease, whether the deficiency is in the nature of food or of necessary metabolites, must be gone into thoroughly.

The management of any case of acute dysentery of undetermined origin is about as follows: In general, the patient should be treated as if he had one of the transmissible forms of dysentery, such as typhoid fever or bacillary dysentery. Diagnostic criteria have been discussed by Doctor Magath, but while the tests to establish the diagnosis are being carried on, some of the precautions that accompany isolation should be applied. Everything leaving the patient should be sterilized; feces and urine should be disposed of properly and containers for all excrement sterilized.

When the diagnosis has been established it may be found that such precautionary measures may be relinquished, or, as in bacillary dysentery, they may have to be even more stringent. In the case of bacillary dysentery, the usual supportive measures described for the severe case of chronic ulcerative colitis are in order. Specific treatment in the forms of administration of serum or bacteriophage and, later, vaccines, should be employed in these cases.

A word about the treatment of the tender anus and prolapsed and swollen hemorrhoids occurring with severe dysentery may be in order. Treatment should be palliative. Operation on such hemorrhoids should be avoided. Local heat, digital replacement, soothing ointments, and local sedatives should be employed for these local anal conditions. Irreparable damage has been known to occur with too drastic attempts to care for such anal conditions when much more serious disease was present above.

In summarizing, it can be said that many serious forms of dysentery and diarrhea afflict the human organism. Many of these are attributable to disease within the intestine, many more are the result of influences extraneous to the intestine. Their management presents many serious and usually individual problems. The unstinted coöperation of the physician in the laboratory, the roentgenologist, the surgeon, and the clinician is required.

SURGICAL TREATMENT OF THE DYSENTERIES*

CLAUDE F. DIXON, M.D.

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IT has been emphasized by those who have spoken before me that treatment of many of the dysenteries is distinctly a medical problem. It is common knowledge, however, that in many instances the passage of blood by bowel is a signal denoting the presence of a condition which necessitates surgical intervention. Such lesions may be inflammatory, malignant, or potentially malignant. Although included in the inflammatory group are tuberculosis and nonspecific granulomas, I shall confined my remarks to those complications which arise in certain cases of chronic ulcerative colitis and which require

*From the Division of Surgery, The Mayo Clinic, Rochester, Minnesota. Prepared as part of symposium but not read at the annual meeting of the Minnesota State Medical Association, Minneapolis, June 25, 1935.

surgical intervention. In discussing the surgical treatment of malignant and potentially malignant lesions which give rise to the passage of blood by bowel, I shall attempt to direct attention to the polypoid tumors of the colon because their presence is so frequently suggested by dysentery.

Essential Operations in Chronic Ulcerative Colitis

It seems worth while to emphasize two points regarding operations for this condition. First, that the need for surgical intervention has been strikingly diminished in our practice since we have employed the treatment which Bargen has mentioned; and second, that operations in such cases entail considerable risk. A decade ago, when the medical treatment of chronic ulcerative colitis was more or less empirical, establishment of an ileac stoma was frequently resorted to. The high risk of this procedure was emphasized by the late Sistrunk. He stressed the dangers of fatal peritonitis following ileostomy in these cases even if the procedure was carried out in a most meticulous manner. When one calls to mind the extensiveness of the ulcerations of the colon in chronic ulcerative colitis, the hazards of peritonitis can be seen.

The necessity for ileostomy in these cases has become increasingly less during the last few years. Of fifty-seven patients treated in 1923, sixteen required ileostomy; in 1932 only one ileostomy was performed. The cases of chronic ulcerative colitis which now require operation are those which are not amenable to medical treatment. A comparatively small group are those in which complications arise, such as strictures and perforations, polyposis and malignancy. It is my opinion that when permanent ileostomy is necessary, the single-barrel type, inverting the proximal end of the distal portion of the ileum, is best. Particularly is this true if the necessity for subsequent colectomy is anticipated. Strictures of benign character may involve only a small length of colon and may occur when the disease is arrested. In such instances, segmental resection can be performed with subsequent reestablishment of the continuity of the bowel.

Perforations frequently require establishment of an ileac stoma and later treatment as indicated. Frequently, enterostomy is all that is necessary. I recently saw a young man, aged thirty-two years, who was suffering from ulcerative colitis. An acute perforation occurred in the hepatic flexure of the colon. Ileostomy was performed and, under medical management, no further operation was necessary. Within a year the entire process in the colon apparently had become arrested and the ileac stoma was closed. The patient made an uneventful recovery, and now, ten months later, he apparently is in good health.

Development of polypi in the colon following ulcerative colitis has been emphasized in a recent publication by Bargen and me. Such polypi apparently result from hypertrophied areas of mucous membrane between the sites of the previously ulcerated areas. Superimposed on these hypertrophic areas, true adenomas may form, with subsequent malignant degeneration. Another site for the development of malignancy in these cases is at the edge of one of the previously ulcerated areas, as Broders has stressed. The majority of malignant growths in the bowel of those who have suffered from ulcerative colitis are of extremely high grade. The incidence of malignancy, as Bargen has pointed out, is 2.5 per cent.

Colectomy occasionally is indicated in ulcerative colitis in those cases in which the condition is intractable. It is also indicated in those in which diffuse polyposis, with or without malignancy, develops. Carcinoma of the colon, superimposed or associated with chronic ulcerative colitis, may be rather diffuse throughout a long length of bowel or it may be local. Obviously the extent of the lesion determines the type of operation to be employed. When total colectomy is indicated, it is my opinion that it should be carried out in three stages: First, by the establishment of an ileac stoma; second, by removal of the colon down to the sigmoid or rectosigmoid, and third, by removal of the remaining portion of bowel. While this procedure is a formidable one, it fortunately is not often necessary.

Malignant and Potentially Malignant Lesions

I now wish to deal with the surgical management of that type of lesion which frequently gives rise to dysentery and which is so often not diagnosed until the symptoms have persisted for some time. I refer to the polypoid type of lesion of the colon. Until the recent improvement in roentgenographic technic, the presence of many

of these lesions could not be determined. There has been considerable discrepancy regarding the origin and nature of polyps and whether or not they were prone to become malignant. Menetrier, in 1888, classified polypoid lesions of the gastro-intestinal tract into two groups: First, discrete polyps, with either pedunculated or sessile independent attachments, which, he stated, consist largely of glandular tissue; and, second, polyps that arise from a common plaque-like base, which are closely packed in orderly rows and resemble the convolutions of the brain. These last apparently are due largely to the hypertrophied layers of the mucous membrane.

The majority of polyps of the colon with which we have to deal are those of the first group, or the adenomatous polyps. The fact that such polyps may become malignant has been accepted lightly by some. Both Robertson and Ewing have stated that in their opinon probably 50 per cent of the carcinomatous lesions of the colon develop from polypi. I shall cite two cases which emphasize this point:

Case 1.—A young man, aged thirty-four years, came to The Mayo Clinic in March, 1932. The important factor in his history was that he had had intermittent bleeding from the rectum for a period of ten years. The blood was never bright red; usually it was clotted and dark. Hemorrhoidectomy had been performed without relief, a procedure which is frequently employed in this type of case. Examination revealed a polyp in the first portion of the sigmoid. The patient refused operation, but an exaggeration of his symptoms caused him to reconsider and, one year later, exploration was carried out. A pedunculated polyp, about 5 cm. in diameter, was found in the first portion of the sigmoid. In the mesentery adjacent to the polyp, an enlarged lymph node the size of a lima bean (about 1 by 1.5 cm.) was removed for diagnosis. No other enlarged lymph nodes were found. The one removed showed adenocarcinoma. Segmental resection was carried out, from which the patient made an uneventful recovery. Two years have elapsed since then and his health remains good. Microscopic study of the polyp disclosed definite carcinomatous change (Fig. 1).

Case 2.—A woman, aged fifty-four years, was admitted to the clinic in January, 1935, because of dysentery of twelve years' duration. During the two years prior to admission her symptoms had become markedly accentuated, and she had passed blood by rectum more frequently and in larger amounts than formerly. Roentgenographic study revealed a single polyp in the midportion of the sigmoid, and at operation, in February, 1935, this polyp in the midportion of the sigmoid was found to have undergone malignant degeneration and to have invaded all layers of the bowel. Segmental resection was performed, and the patient's convalescence was uneventful. On examination the polyp was found to be definitely malignant (Fig. 2).

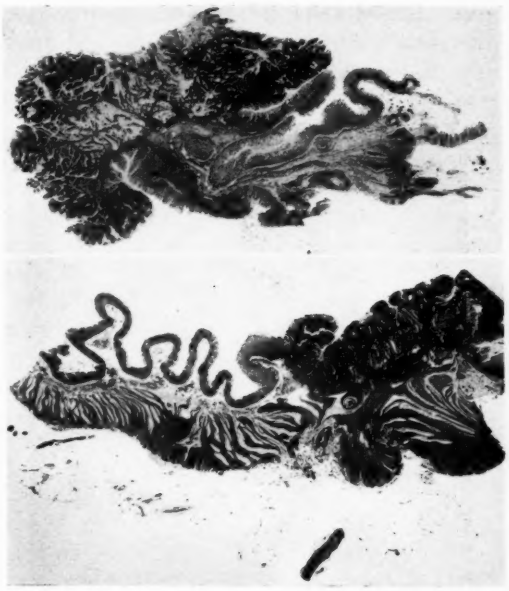

Fig. 1 *(above)*. Case 1. Section of pedunculated polyp from first portion of sigmoid, showing adenocarcinoma.

Fig. 2 *(below)*. Case 2. Sessile polyp of the sigmoid, showing carcinomatous degeneration.

I cite these two cases to emphasize two points: First, that these lesions frequently are the cause of dysentery and may easily be overlooked, and second, that they do become malignant. It is true that many polypi of the bowel are benign, at least in the beginning. It seems fair to postulate in these two cases that malignancy was not present during the entire period of dysentery. Malignant degeneration of a polyp usually begins at its periphery, according to Robertson, and may gradually involve the stalk and later the various layers of the bowel. For those malignant polyps which are pedunculated, removal at the base of the pedicle would probably be sufficient to effect a cure, providing the malignant process had not gone beyond the site of amputation.

Diffuse polyposis of the colon is a condition which is not as common as was formerly supposed. In those cases which we have had an opportunity to study, malignancy almost invariably developed. In many instances, diffuse polyposis is hereditary. Colectomy has been carried out in such cases when four or five distinct carcinomas were present. Whether or not malig-

nancy is present in diffuse polyposis, the condition usually gives rise to such a marked dysentery that surgical intervention is necessary. A case in point is the following:

Fig. 3. Case 3. Section of colon showing diffuse polyposis.

Case 3.—A woman, aged twenty-four years, came to the clinic in January, 1934, because of profuse hemorrhages from the rectum. Examination revealed diffuse polyposis of the colon (Fig. 3). The lesions were not pronounced in the rectosigmoid or in the rectum. Colectomy was performed, preserving the lower portion of the sigmoid and rectum. The first stage of the procedure consisted of ileosigmoidostomy; the second stage consisted of removal of the entire colon up to the site of the previous anastomosis. The lower part of the bowel was preserved because many of the polypi removed at the time of proctoscopic examination proved on microscopic study to be benign adenomas. It was felt that the remaining polypi in the rectum and rectosigmoid could be dealt with by fulguration.

Preservation of the lower portion of the sigmoid and rectum in this case probably was unwise. It did obviate a permanent artificial anus, to which the patient objected.

Summary and Comment

In this paper I have not attempted to discuss all the instances in which surgical treatment of lesions causing dysentery are indicated. The operations which are essential in chronic ulcerative colitis have been greatly decreased. Those which we find necessary have been referred to.

Polypoid lesions of the colon, so often the cause of bleeding, are briefly discussed, and the tendency of such lesions to become malignant is emphasized.

REMINISCENCES OF A RANGE PHYSICIAN

C. W. MORE, M.D.

Eveleth, Minnesota

BEFORE I began the study of medicine, I was connected with a drug store in a small town in Iowa. I often talked with the village doctor, an honorable and ethical practitioner, noted as an obstetrician. Those of his patients needing surgery were referred to a surgeon in a nearby city. I recall, about 1883, his showing me a dram vial containing one grain of cocaine in solution, for which he paid $1.00.

About 1882 or 1883, I remember one patient, the village blacksmith, with greatly enlarged glands of the neck. Some of the glands, when removed, were found to be the size of a small hen's egg and filled a one-quart fruit jar. The surgeon who operated took no aseptic or antiseptic precautions. He operated with bare hands, without special attempt at cleanliness. He did not suture the wound but packed cloth soaked in olive oil into it for a dressing and continued this treatment daily for weeks.

Another patient, a farmer's boy, with necrosis of the femur, was operated on at his home. The country doctor gave the anesthetic—ether. He took me with him to pour the ether into the mask, which was made by rolling a newspaper in the shape of a cone and stuffing a towel into it on which to pour the ether. Infection was beginning to attract attention and was thought to come from the air. The surgeon, who operated on the boy, attempted to carry out the then latest protective method by having a spray of 5 per cent carbolic acid in water from a small

cheap steam atomizer passing over the leg and surroundings during the operation, until it went out of commission. After he had exposed the bone, he asked the other doctors, including the anesthetist, to feel of it. He then asked me to feel of it. I, as I had seen the others do, put my fingers in the wound without washing my hands.

In 1885, a few days before college opened, I arrived in Chicago to begin the study of medicine. I had the privilege of seeing one of the leading surgeons of Chicago, and Professor of Surgery of the Chicago Medical College, operate at Mercy Hospital. The doctor wore a heavy beard. The operating table was a plain wooden affair. The seats of the amphitheater were also of wood. The surgeon came in, removed his coat, put on an old Prince Albert coat, which was kept hanging on a hook nearby for that purpose, took the instruments out of the bag, and went to work without any further preparation. He examined the patient's mouth with bare fingers, pulled an upper central incisor tooth, made the usual incisions and removed the left upper maxilla skillfully and without hesitation. This is a fairly accurate description of other operations witnessed during the year. These old-time surgeons were skillful and rapid.

Before I graduated, there was some attempt at antiseptic technic. Dr. Ralph Isham, another professor of surgery, gave us a rather dry lecture on the germ theory, as then understood, and told us about experiments being carried out on mice.

Some of the older men who had practiced medicine forty or fifty years and had seen and experienced many innovations, suggestions, and recommendations advanced at various times, a few of them good but most of no value, were rather skeptical about the germs being responsible for infection. The younger men connected with the college were favorably impressed with the theory.

During my senior year, I was second or student assistant to the chief surgeon of the Chicago and Northwestern Railroad, Dr. Owens, where the latest methods of caring for injured railway employees were carried out. Open wounds were irrigated with a solution of 5 per cent carbolic acid or 1-1000 bichloride of mercury, then dusted with powdered iodoform and wrapped with unsterilized gauze or cotton. The wounds were dressed frequently, often daily.

After serving as assistant to Dr. Shipman, a mine physician, at Ely, for five years, I resigned, took a ten-weeks' postgraduate course in New York, and then located at Eveleth in June, 1894, as physician for the mine and railroad employees. The town had been started the year before, but hard times had come on and it was partially deserted. When I arrived there was a saloon, a boarding house, three or four families and a few shacks and tents, where some of the miners lived.

With borrowed money, I bought a few drugs and dressings, a second hand bed spring, a cheap mattress, moved into an unfinished and abandoned saloon shack and took my meals in a large tent with the other mining employees. This dining tent was located near a small creek one could jump across. A hole had been dug near it by the proprietor of the tent, who was also the cook, to furnish water for washing clothes, dishes, et cetera. The summer was hot and dry. The inside top of the tent was black with flies. Countless fly specks on the plates we wiped off as best we could with bread, before placing food on them. Typhoid fever resulted. The sick were cared for in tents, shacks, or wherever they lived. I was doctor and nurse, bathing the men, shaking out the dirty and dusty blankets and sheets, if they had any. Most of the patients ran a temperature of 104 or 105. Some had complications.

My first and only pay day during the entire summer netted me $48.00 plus board in the tent.

By September the weather was getting colder and I borrowed $25.00 and bought a wood burner box stove and two blankets. George Watts and D. B. Austin, civil engineers, living under much the same conditions in another camp, helped me cut some wood. My attempt to split wood tired me. I had been running a low temperature for about three weeks but kept going until one morning, three days after I bought the stove, I did not have enough ambition to get up until someone came and wanted to know why I did not go to see my patients. I was weak, could hardly stand, temperature 105 at 10 A. M. I realized I was through.

I was sent to St. Mary's Hospital in Duluth where Dr. S. H. Boyer took care of me for two months. After leaving the hospital I was

laid up with phlebitis at my father-in-law's home, in Milwaukee, for three months.

I returned to Eveleth with my wife in February, 1895. There had been an number of buildings put up: two double two-story buildings, one of which was used as a hotel by Mr. Charles Jesmore, the other a drug store and clothing store with rooms and office upstairs. We lived in the hotel and I rented the only available room over the drug store for an office; and so I went to work again, considerably handicapped this time by being obliged to use a cane.

I kept, as an assistant, the young physician who had been looking after the work during my absence. We had no hospital, but there was an empty, one-story building, boarded on the inside of the studding only, which we made habitable by boarding up to the ceiling of the first floor on the outside and nailing some building paper on the inside and filling the space with sawdust. We put up two beds and heated the room by the box stove I had bought five or six months before. This makeshift answered for a hospital for several months, when I had another one built—twenty-five by forty feet, one-story, but warmer, and plastered and filled with hospital beds. At one time we had nine patients with fractures, including a broken spine and a crushed pelvis.

* * *

Meals were brought from a nearby boarding house. This building served until 1900, when we moved into the present building, to which two additions have been made.

During the earlier years of my practice, before antitoxin was discovered, I had the same experience that many doctors have had with little diphtheria patients. Mild cases convalesced in one to three weeks; others died. In the so-called croupous cases, the exudate developed in the larynx primarily or by extension; a few would recover after a stormy time but all too frequently, in other cases, the throat would fill up, respirations would become more and labored, and the child die of asphyxiation or exhaustion. Tracheotomy was frequently resorted to with varying results. Then O'Dwyer presented the medical profession with the intubation tube, to be put in the trachea through the mouth. About 1894, while taking the postgraduate course in New York, I received practical instructions in its use on baby cadavers. To use it, the child was wrapped firmly in a sheet and held in someone's lap, who placed one arm around the child and, with the other on the forehead, held the head against his shoulder. A gag held the mouth open and the tube was quickly inserted into the trachea and what a relief it was to the parents and the doctor to see the child breath easily and drop off to sleep. That was ideal. Unfortunately, it could not always be obtained. Sometimes the tube could not be placed so easily; occasionally the throat would be so filled with exudate that some of it would be pushed down ahead of the tube, plug it up so that the child could not breathe and tracheotomy was quickly resorted to, but too often the baby's big round eyes would roll toward me, the head would fall to one side and the baby was dead. I hope none of you will ever witness such a picture. We older ones have reason, by experience, to appreciate, and be thankful for, diphtheria antitoxin and other modern means to prevent or cure contagious and other diseases.

The history of diphtheria, or putrid sore throat, as it was sometimes called, and its clinical symptoms, is interesting reading.

I will omit the details of my first thigh amputation on the Range, except to say it was done at 11 P. M. The young man who did chores around my house and office and took care of my horses handled the anesthetic after my associate had gotten the patient to sleep. The night policeman held the small kerosene lamp and the amputation was quickly done by the transfixion method.

* * *

The following was reported to me as occurring during the nineties. A miner at Soudan, Minnesota, had a badly united fractured arm and threatened to sue the mining company unless the arm could be made useful. The mining company doctors attempted to correct the deformity, but the patient died on the operating table. The doctors, after using every means to resuscitate him, passed a needle between the ribs to his heart in a desperate attempt to stimulate it to action. His wife, who was present, quickly spread the story among the people of her nationality that the doctors could not kill him fast enough with the chloroform and stuck a knife in his heart, and they threatened dire vengeance against the doctors. It was reported that the doctors carried revolvers for some time

afterwards as a protection, but I cannot vouch for it.

One evening in the early fall of 1897, a few years after I heard the above story, I was summoned to a boarding house to see a man called Oscar, who had supposedly shot himself. Arriving, I noticed twelve to fifteen men sitting in chairs on the side of the room. None offered me a chair and nothing was said as I entered. When I inquired where the patient was, one man pointed to a man lying prone across two chairs near the kitchen stove, his head extending over the woodbox to catch the blood from the wound. After getting him in a sitting position, I saw that his right eye was swollen shut and ecchymosed. I said, "A fight?" Some man said, "No, shot," and pointed under his own chin. Examination under the patient's chin showed powder marks and a bullet hole, from which blood trickled. There was a hole through his tongue and the roof of his mouth. When he tried to swallow the fluid would pass through the hole in the palate to his nostril and this made him angry and irritated him. While examining the head for evidence of an exit for the bullet, I found a large hole in the back part of his head. Someone said he had had that before. More careful search revealed crepitus and a loose bone in the upper part of his forehead in line with the bullet holes. I gave him some mouth wash and left.

The next morning someone came for me and said Oscar's friends wanted something done. My associate and I responded. As we entered the house, we noticed a self-appointed jury of twelve men sitting in two rows of six each in a corner of the room. I realized at once that they had formed a jury to watch my operation with the intention of preventing a recurrence of the incident at Soudan.

As a matter of self protection, I told the foreman of this jury, who could speak English, that the patient might die, and if I said, "Raise him up," he was to have four men instructed to step up on the table and raise him up in an inclined position with head down. The patient was placed on one end of the twelve to fourteen foot dining table in the kitchen and given ether. As I made the preliminary curved incision, the patient stopped breathing and I turned to the jury and said, "Raise him up." Four men stepped up on the table and quickly did as I had instructed them. Following artificial respiration and a hypodermic of strychnin, respiration was restored and the bullet, with a few pieces of bone, was removed and the wound stitched. The patient made an uneventful recovery but was greatly annoyed by the fluid passing through the roof of his mouth to his nose.

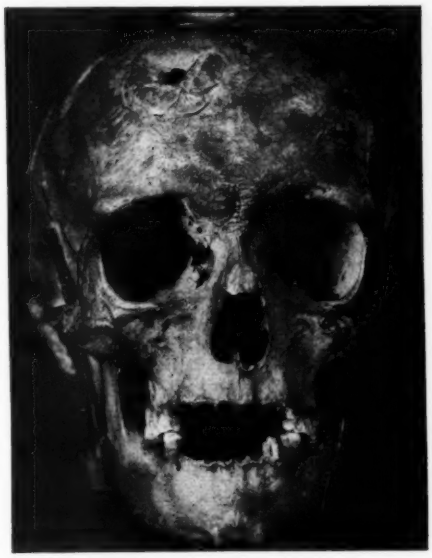

Fig. 1. Skull showing bullet hole in frontal region.

Two or three months later, some of his friends came to me to inquire if I knew what had become of him. They said he had started for Ishpeming but never reached there. I knew nothing about him.

About two years later a skeleton was found in the woods, not far from the sporting houses, which were to be found in every mining village. There was a piece of rotted rope hanging from a limb of a tree above. The shoemaker recognized the heel of the rotted shoe as belonging to my former patient. Some of the curious who viewed the skull advanced the theory that he had been shot in the nearby sporting house while in a stooping position; that the bullet had entered the forehead and had come out from the large hole in back and that the rope on the limb had been placed there as a blind.

A sheriff came up from Duluth to investigate. He asked me to go to the undertaker's in Virginia to see if I could identify the skull. Fortunately I had kept the bullet and pieces of bone.

As they fitted nicely there was no mistake as to his identity. I asked the undertaker if there was to be a funeral. He said no, a county case. I asked if I might have the skull. He said he had no right to give it to me, but that he had to go up town.

* * *

Before the high pressure steam sterilizers were known, the early method of sterilizing dressings was by boiling or using low pressure steam. My first sterilizer was an Arnold low pressure, and dressings had to be exposed to the steam for two hours at twenty-four hour intervals for three days. The steam was supposed to destroy the fully developed germs but not the spores, which did not become fully developed until forty-eight hours after the first steaming.

Another method was to boil some cheesecloth to get rid of the sizing and starch, cut, fold, and roll it in suitable sizes and soak it in 1-1000 bichloride for twenty-four to forty-eight hours, wrap it in waxed papers. These my wife helped me to make. The gauze was then kept in boxes ready for use.

During the early days, the Range towns had no municipal water supply or sewage, and slops and refuse of all kinds were deposited on the ground in the alleys. The alleys consequently were filthy. It was impossible for the village scavenger to keep them clean, and often slops would run into the neighbor's yard, and, in the summertime, flies swarmed the alleys and kitchens and spread disease, especially typhoid fever. In desperation, at my request the village trustees passed an ordinance, prepared by an attorney, compelling people to build a raised platform in the alley and to keep a covered receptacle on it and to deposit their slops or refuse in it and to use lime. The scavenger could now easily remove the slops for the entire village in one day and the alleys were kept clean. Some of these stands were rather unsightly and caused some criticism and amusement. While this method was rather crude, it was the best we could do at the time.

If I should attempt to tell my experiences with hundreds of cases of typhoid fever, with its many complications, it would take too much time and space.

Walking several miles in rubber boots, in order to cross a creek or swamp, to see a patient, or skating across the lake in the early fall, before the ice was strong enough to hold up a horse and cutter, with a satchel strapped over the shoulders, or walking six or eight miles through the woods to an exploring camp, following a trail sketched out by the civil engineers of the mining company, or helping carry a sick woman through a bog or swamp along a lake shore to a boat, in order to get her to town, were the common experiences of any pioneer doctor and were not considered a hardship.

* * *

I will report a case of prolonged pregnancy that emphasized what nature will do if given an opportunity. A woman of rather short stature, the mother of several children, consulted me regarding the delay in her expected confinement. From her history, she was about two weeks overdue. Examination apparently confirmed her story and she was advised to wait with patience. Almost three months later, I returned home after one week's absence and was met at the railroad station by one of my associates who informed me I would have to do a craniotomy. He said the woman had been in labor three or four days, with no apparent progress, for the past twenty-four hours. He admitted that the babe was viable. It was the woman I had seen three months before. I had never done a craniotomy on a living babe and I could not reconcile myself to do it now. I cannot describe the horror I felt, and I resorted to various expedients to delay the ordeal. After two hours, I drove to the patient's home. Lo and behold—the baby's head had come down on the perineum, much to the surprise and delight of the attending physician as well as to myself. It was an uneventful delivery. The head was full size, round, hard, had not moulded while passing through the pelvis and the fontanels were hardly discernible. This helped to confirm the patient's history of a prolonged pregnancy or delayed delivery.

Mrs. A. C., aged thirty-six, the mother of two children, consulted me in 1905 for some distress in the lower abdomen. I am unable to locate the history giving her symptoms. There probably would be nothing of value in it. Examination revealed a firm, slightly movable tumor to the left of the uterus, which, upon being removed, proved to be a lithopedion about the size of an orange. It was confined within the

left tube, which was stretched over it as thin as a rubber glove would be. After removing the tube with the tumor intact, I drew a knife across it and the thin tube retracted quickly and completely as though it had been a piece of fresh rubber.

* * *

One New Year's evening, as I was returning to my office over the drug store, I was met by some anxious citizens saying that a man with smallpox had been brought to town from a logging camp a few miles from Eveleth, and that he was in a jumper over there, pointing to the place. (A jumper, as you probably know, is a sled with runners about eight or ten feet long and usually drawn by one horse.)

The man was warmly covered with blankets. I uncovered his face, felt of it, examined it by lantern light and easily confirmed the diagnosis.

As the town had been recently moved from the hollow to its present location, every building was occupied. There was not even a vacant shack in which to put the man. I advised the driver to take him to Virginia, as I knew they had a place for such cases. In about two hours they returned, said the doctor, or health officer, told them he belonged to Eveleth and sent them back here.

After consulting with the village officials, the only alternative left for us was to direct them to return to the camp with a promise that a doctor would drive out there the next day and see him. After prescribing for him, they started back.

In the meantime, the Township and Village trustees hastily swore in a number of deputies and, under the supervision of the Chief of Police, armed them with rifles and sent them out to quarantine the camp of about seventy-five men ("lumberjacks"), as required by law. Some of the men naturally resented this measure, especially the cook, so it was reported, who would shout at the guards through an open window, calling them names and threatening to shoot them if he had a gun. Some of the guards afterward admitted feeling nervous and under tension.

We were very busy the following day and, before we could leave, a messenger came in for a doctor, saying a man had been shot. Dr. A. W. Shaw, now of Buhl, a man of good judgment, and I, drove to the camp. It was a beautiful moonlight night. As we approached the camp we could see the flare of bonfires at various places through the trees.

The guards were standing about on duty and halted us until they recognized who we were. As we went into the foreman's office, the first

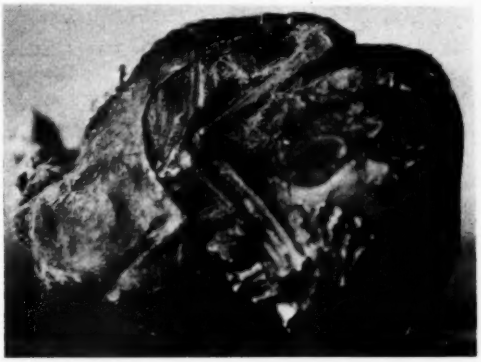

Fig. 2. Lithopedion.

thing that met our eyes was a dead man on the floor. We made a casual examination, so as to report. The foreman's greeting was something like this, "You are a blankety blank bunch of men to shut us up and shoot us down like dogs." We could not blame him. We told him we were there as doctors and not as officers and asked him to go with us into the main camp, but he refused. Dr. Shaw and I went into the camp. Our reception was perhaps not the most friendly, rather tense at first.

Our first act was to see the patient, who was occupying an "upper berth." We then asked the man in the bunk below if he had ever been vaccinated. He replied "No." As we explained the advantage of vaccination, some gathered around and appeared interested and favorably impressed; others were inclined to make trouble, to "act smart" as it were. One said he had been vaccinated "and had nearly lost his arm." The same story you all have heard over and over. He showed us a large scar on his arm and we agreed with him that he had had a hard time of it and that he had gotten it infected, probably by scratching it. It was not wise to get into an argument with these men. Before we left, we had vaccinated between fifty and sixty men.

It seems that the man who was shot was in the stable with others, helping take care of the

horses. When the dinner horn sounded he did not leave immediately, so one of the guards ordered him in. He started toward the guard, who slipped a cartridge in his gun and shot him. The guard was arrested and tried, of course, and the woodsmen testified against him. The judge understood the situation and said, "If you were younger, I would sentence you to the reform school," but as it was he sent him to the penitentiary for an indefinite period. As he entered the prison, the warden greeted him with, "Hello Anderson! You back again?"

It pays to select our officers, especially policemen, with care.

LATENT SYPHILIS*

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SINCE the advent of malariotherapy there has been considerable discussion of the defensive mechanism of the syphilitic, much more in fact than at any time since Ehrlich introduced salvarsan, in 1910. At that time, it was expected and hoped that a specific agent for the treatment of syphilis was at hand; however, two decades have now passed, and experience has proved that arsphenamine does not possess all the qualities of the ideal specific. To be thoroughly efficient in the treatment of early syphilis, arsphenamine must be augmented by either bismuth or mercury; thirty injections of arsphenamine with twice as many injections of one of the heavy metals will result in the cure of approximately 80 per cent of the patients who have early syphilis. In the malignant types of the disease, such, for example, as general paresis and aortic disease, the curative effect of arsphenamine is but slight. Between these two extreme types, the benign forms of syphilis of the skin or bone may be cited as examples of lesions in which arsphenamine, when combined with mercury or bismuth, results in the rapid healing of and arrest of the disease process in most of the cases. In brief, then, it may be said that in cases in which the parenchymatous complications of the disease have become manifest, arsphenamine seldom prevents the progress of the condition, although in cases in which the less vital structures are involved, the complications are less serious and the results from the use of arsphenamine are usually most satisfactory.

It is the purpose of this paper to call attention to that phase of syphilis known as latent syphilis, which may be defined as that period of the disease when neither clinical signs nor symptoms are present. It may also be thought of as the concealed phase of syphilis. In the study of the Coöperative Clinical Group latent syphilis was divided into the early and late forms. Early latent syphilis includes those cases in which syphilis has been present for less than four years, while late latent syphilis includes those cases in which the disease has been present for more than four years. The reason for this subdivision is the fact that in the majority of cases of syphilis there is evidence of an effort of a defensive mechanism to develop in the first four years of the disease. An illustration of this is the tendency of the spinal fluid of many patients with asymptomatic neurosyphilis to become negative spontaneously by the fourth year of the disease, and the fact that the infectious types of clinical relapse seldom appear after the fourth year. On the other hand, after the disease has been present for four years, the incidence of the clinical manifestations of neurosyphilis increases each year thereafter. The study of the Coöperative Clinical Group and the report of Bruusgaard offer evidence of the fact that syphilis sometimes is controlled spontaneously.

Latent syphilis also has been divided into clinical, serologic, and pathologic latency by Moore, and it will be considered briefly under these headings.

Clinical Latency

Clinical latency exists when no clinical signs or symptoms of the disease are discernible. This does not imply, however, that syphilitic invasion

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of the viscera has not occurred, because when the aorta or liver is only slightly involved, signs and symptoms are absent. These manifestations of syphilis may remain slight and the patient may be asymptomatic for years. Accordingly, the line of distinction between clinical latency and asymptomatic visceral syphilis may not be well marked, and at times constitutes a difficult diagnostic problem. Latent syphilis clinically may follow one of two courses: It may remain as such for the rest of the patient's life, during which he will remain free of symptoms and signs of the disease. On the other hand, visceral syphilis may become recognizable after several years of such latency. The important point to bear in mind in regard to the management of syphilis, which is latent clinically, is that in some of these cases extensive treatment is warranted, while in others only observation and frequent reëxamination are indicated. In the consideration of the treatment of latent syphilis, this point will be considered in detail.

Serologic Latency

Serologic latency implies that although the serologic tests are negative the patient still has active foci of syphilis. Ten years ago, when the serologic technics were less sensitive than they are at present, serologic latency was very common. However, with the newer flocculation tests, serologic latency is a phase of syphilis which is now encountered less frequently than it was in the past. With the advent of more sensitive serologic technics, which no doubt will be developed in the future, serologic latency will be even less common than it is now.

Pathologic Latency

Pathologic latency means that active Spirocheta pallida are present in tissue but that a pathologic reaction on the part of the host to the invader, in the form of a minute or massive gumma, is lacking. This conception of latency was fostered by Warthin, who demonstrated Spirocheta pallida in the cardiac muscle and testes of latent syphilitics, in the presence of mild pathologic changes. For some time, this was the basis for the conception that latency was characterized by the development of nests of Spirocheta pallida which might remain dormant for years, or might at any time become active and produce clinically recognizable manifestations of the disease. The proof that the state of pathologic latency exists is dependent on the findings at necropsy, and is a pathologic problem which is still subject to debate.

Diagnosis of Latent Syphilis

The diagnosis of latent syphilis is made by the process of exclusion, as such a diagnosis can only be made after careful search has failed to elicit any evidence of syphilitic disease of the viscera or nervous system. A history of the primary or secondary manifestations of syphilis helps to place the disease either in the early or the late phase of latency, and if the history of primary or secondary syphilis is lacking, a classification into early or late latency may not be possible. An examination of the spinal fluid is essential for a diagnosis of latency. If the reaction of the spinal fluid is positive, the diagnosis of latency is immediately discarded, and the type of neurosyphilis, such as asymptomatic, cerebrospinal, or parenchymatous, is sought. If the serologic tests on the blood and the reaction of the spinal fluid are negative, and if the history reveals evidence that the patient has had an acute syphilis which was adequately treated, and if no signs of syphilis are manifest, the diagnosis of latent syphilis may be made. On the other hand, if the serologic tests on the blood are positive and if the reaction of the spinal fluid is negative, and if there is a history that the patient has had acute syphilis which was adequately treated, the diagnosis of latency is possible only after a thorough clinical examination has failed to disclose evidence of syphilis. Such an examination should include careful scrutiny of the cardiovascular system, including roentgenologic examination for evidence of aortic enlargement; and examination of the nervous system, fundus oculi, the viscera, and the osseous system, for signs of syphilis. The mucous membranes must also be scrutinized because syphilitic leukoplakia frequently may be the only clinical manifestation of syphilis. If such a detailed examination fails to elicit involvement of any of the systems mentioned, in the presence of a negative reaction of the spinal fluid, the diagnosis of latent syphilis is warranted, even though the serologic tests on the blood remain positive.

Mention already has been made that the patient who has latent syphilis should either be

treated or placed under observation. The study of the Coöperative Clinical Group showed that if a group of latent syphilitics was observed for ten years, spontaneous cure would be noted in from 25 to 35 per cent; in an additional 25 to 35 per cent, the patients would remain Wassermann-fast; in 10 to 15 per cent, late syphilis of either the skin, mucous membrane, or bones would develop; in 10 to 15 per cent, cardiovascular involvement would be noted, while in 1 to 3 per cent, syphilis of the central nervous system or viscera would become manifest. As there are numerous factors which influence the decision as to whether a patient with latent syphilis should be treated or not, I shall report several cases which emphasize the significant reasons for the therapeutic program of this phase of syphilis.

Report of Cases

Case 1.—A farmer, aged sixty-five years, had acquired syphilis thirty-five years ago. The syphilis had been recognized at that time, the chancre had been cauterized chemically, and some mercury pills had been taken at irregular intervals for less than a year. He had married ten years after he had acquired the infection; his wife never had become pregnant. He came under my observation because of a positive Wassermann reaction on the blood, which was discovered in the course of an examination preliminary to surgical repair of bilateral inguinal hernias.

The physical examination demonstrated bilateral inguinal hernias, but examination of the cardiovascular system, including a roentgenologic study, did not reveal any abnormality. The neurologic examination and the examination of the ocular fundi did not reveal anything abnormal. No history or findings of visceral disease were elicited. The mucous membranes did not show any evidence of leukoplakia. Examination of the spinal fluid did not reveal any abnormality.

In brief, this is the story of a sixty-five-year-old man who has had syphilis for thirty-five years and now has only a positive Wassermann reaction to show for it. It is known that practically all the serious sequelæ of syphilis are manifested clinically between the twelfth and eighteenth years following the acquiring of the disease. As this patient has had the infection for thirty-five years and does not present any clinical signs of syphilis, the probabilities are that no serious complications of syphilis will develop from this point on. Examination of his wife, which included a Wassermann reaction of the blood, did not reveal anything abnormal.

As the absence of signs and symptoms of syphilis was more significant than the positive Wassermann reaction, the patient was placed under observation or "on parole." He reported for annual examinations, particularly of the cardiovascular system, and as the examination failed to reveal anything abnormal in three years, he subsequently was discharged. There is no indication to attach significance to this positive Wassermann reaction; in fact, repetition of the serologic test at each annual examination is not necessary, because the positive report "per se" is of no significance. In this type of case, the importance of the serologic report should be minimized. "Do not treat the positive Wassermann." In such a case, if any of the annual examinations arouse suspicion that the syphilis has produced visceral disease, treatment may be instituted immediately.

Case 2.—A widow, aged forty-two years, came to the clinic because of disease of the gallbladder. Although her husband had died five years previously of aortic aneurysm, no history of primary or secondary syphilis could be elicited. Since her marriage twenty years previously, she had become pregnant three times; the first two pregnancies had ended in miscarriages, and the third pregnancy had terminated in a stillbirth. She had had a pelvic operation three years after the last pregnancy, when both fallopian tubes and one ovary had been removed.

The physical examination revealed an obese, middle-aged woman. Roentgenologic examination of the gallbladder showed the presence of gallstones. The serologic test on the blood was positive, but the spinal fluid was negative in all factors. The examination of the cardiovascular and neurologic systems did not reveal anything abnormal, and no evidence of syphilis was elicited in the eyes, bones, or mucous membranes. The syphilologist could find no objection to proceeding with surgical operation. The gallstones were found and removed; an examination of the liver did not show any signs of syphilis. The convalescence was uneventful.

A widow, aged forty-two years, probably had acquired syphilis from her husband, shortly after her marriage twenty years previously. She presented only positive serologic tests on the blood. She had never received any antisyphilitic treatment. Perhaps criticism would be made of permitting such a patient to undergo an abdominal operation from the standpoint that the surgeon would be subjected to the risk of infection and that the patient might encounter postoperative complications in the healing of the wound. In answer to the first criticism, sufficient evidence

is now at hand to warrant the statement that when syphilis has been present ten or more years the condition is not infectious, to all practical purposes. The likelihood that the surgeon or his assistant would acquire syphilis from such a patient is very slight. In regard to the effect of operation on a patient who has latent syphilis, my experience has impressed me with the fact that the danger therein is twofold: first, the effect of the surgical trauma on a syphilitic process elsewhere than at the operative site; and second, the surgical disturbance of a gummatous process. For example, an unrecognized aneurysm may rupture as a result of operation which involves the abdomen; on the other hand, if the mass for which the operation is performed is gummatous, healing of the wound will not occur as the gumma will recur and extend rapidly. In the case under consideration, the evidence of visceral syphilis was lacking, and the removal of the gallstones was warranted because of frequent colics.

Following the operation, the presence of syphilis was discussed with the patient and an effort was made to minimize the positive serologic test on the blood, but only after she had agreed to report for annual examination. Three years after the cholecystectomy, and shortly after she had completed the menopause, she sought our approval in regard to marriage. Our approval was readily granted. Reëxaminations have been made at irregular intervals for the past ten years. She has not infected her husband, she has never had treatment for the syphilis, and the serologic test on the blood has now become negative. In the Coöperative Clinical Group's study of latent syphilis, it was shown that in 83 per cent of a group of cases of latent syphilis which was observed for ten years or more, the reaction of the blood became negative spontaneously.

Case 3.—At the age of twenty-four years, a woman had been divorced from her first husband because of his infidelity. She had become pregnant once, but there had been a spontaneous miscarriage. Shortly after her divorce, she had been found to have a positive Wassermann reaction of the blood, for which eighteen injections of neoarsphenamine and thirty mercurial inunctions had been administered. Five years following this treatment, at the age of thirty years, she consulted me in regard to remarrying. The serologic tests on the blood were positive, but the spinal fluid was negative in all details. Examination of the cardiovascular system did not reveal anything abnormal, and no clinical evidence of syphilis could be found. In the discussion of the situation with her, it was obvious that she was anxious to have a child; in fact, she was opposed to the use of contraceptive measures of any sort. Accordingly, she was urged to continue with treatment and to postpone her marriage for three years. The treatment suggested consisted of two courses of bismuth, twenty injections to the course, each year for the following three years. At the end of the administration of the bismuth the reaction of the blood for syphilis had become negative and she was married. She has not as yet become pregnant.

The significant features of this case are the following: Positive serologic tests are more common in those cases in which patients receive not only an inadequate amount of arsphenamine, but, particularly, an insufficient amount of bismuth or mercury, than they are in other cases. Secondly, it is significant that, in cases of latent syphilis in which the infection is more than four years old, the intensive use of bismuth is rewarded by a higher percentage of reversal of the serologic test on the blood to negative than when arsphenamine is administered and the bismuth is omitted or administered in a small number of injections. A third point, not brought out by this case but nevertheless worthy of emphasis, is that 17 per cent of the pregnancies in cases in which there is late latency will result in syphilitic children. Accordingly, if this patient becomes pregnant, she should undergo intensive treatment with arsphenamine and bismuth, even though the serologic test remains negative, in order to assure her of a nonsyphilitic child.

Conclusions

1. Latent syphilis may be divided into early and late latency, according to the duration of the syphilis, as during the first four years of the infection the patient is in the process of developing a resistance to the disease.

2. Latency is diagnosed by the finding of a normal spinal fluid and the complete absence of clinical signs or symptoms of syphilis. A negative or positive Wassermann reaction of the blood is an insignificant factor in the appraisal of latency.

3. The need for the treatment of latent syphilis is dependent on the duration of the syphilis, the age of the patient, the absence of clinical signs or symptoms, and the possibility of pregnancy, rather than on the status of the blood.

4. Latent syphilis tends to produce negative serologic tests when observed for a ten-year pe-

riod. The highest incidence of reversal of the serologic test on the blood to negative in latent syphilis occurs following the intensive use of bismuth, augmented by a comparatively small amount of arsphenamine, given by the continuous or modified continuous system of treatment.

5. Latent syphilis, diagnosed by exclusion and elimination of all possible complications of syphilis, tends to remain latent in the majority of cases.

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THE LOW BACK PROBLEM*

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THE subject assigned to me is "Low Backache, Sciatica, Congenital Abnormalities, Posture, and Sacro-iliac Strain"—in fewer words, the Low Back Problem. The diagnosis of low back pain is one of the most difficult in orthopedic surgery; but these days of automobile accidents with their pending litigation, of compensable industrial injuries, and of governmental relief make the problem still more complex. Now-a-days the surgeon must look askance at subjective complaints in many of these cases because of possible legal complications which may follow. Not only must the true cause of the pain be determined and treated, but often the extent of aggravation of pre-existing dormant disease must be estimated. In most cases the problem can be solved by a careful history, a thorough physical examination of the back, good x-rays, a clear understanding of the pathology common to the region, and a vast amount of patience.

The history must be carefully taken, and it must be recorded, to be of value, for frequently a legal mind can bring out a history quite different from the one given the surgeon. Previous illnesses should, of course, be noted, especially rheumatism and venereal diseases. The history and dates of previous accidents, fractures, and operations is very important. The exact date (and mode) of onset should be established if possible, and, if traumatic, whether such trauma operated directly or indirectly. In accidental cases Liniger's postulates, given by Kessler,[7] should be considered as follows:

1. The accident must be proved without doubt.

2. The injury must be sufficiently severe to cause immediate cessation from work.

3. The symptoms must appear immediately (or within a few days) after the accident, and persist continuously.

Etiology

Assuming the complaints to be true, one must consider their possible and probable etiology. In the lower back the fascia, muscles, nerves, ligaments, articulations, and bones are to be considered, and each of these tissues is subject to its own host of pathological changes.

Arthritis.—The commonest cause of low back pain is osteoarthritis. This is conclusively shown by the statistics of Miltner and Lowendorf.[10] When arthritis is present the surgeon often must determine whether it was produced by trauma, or aggravated by trauma to a disabling degree. One must be cautious to be fair in cases where litigation is involved, and remember that an aggravation, per se, must ultimately heal; and that a spondylitis may pass through its dormant period and progress to ankylosis without any trauma at all.

Posture.—Excluding arthritis, general toxic conditions, and neoplasms, the effect of faulty posture on the lower back is probably next in

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importance. Whether increased sacral inclination is the cause or result of faulty mechanical use of the body is still being debated, but there is no doubt that the increased sacral inclination present in most individuals puts the lumbo-sacral articulation at a mechanical disadvantage. Poor abdominal musculature permits increased sacral inclination and as this inclination increases beyond the average of 42 degrees, the strain is thrown first upon the ligaments, which stretch under chronic stress, and next upon the articulations. Following Wolf's law, that form depends upon function, the intervertebral disc between the fifth lumbar vertebra and the sacrum becomes more wedge-shaped and much of its shock-absorbing function is lost. Dickson[2] found that 35 per cent of his cases presented "such an architecturally weak articulation" and considered it the "causative factor, not only in predisposing the lumbo-sacral joint to injury, but in the persistence of symptoms."

Anatomic Variations.—Congenital abnormalities, or anatomic variations, are very common in the lower back region, and there has been such controversy about their importance in cases of low back pain. George[2] found that "35 per cent of all spines x-rayed for any purpose showed congenital abnormalities," but common sense dictates that the large majority of these do not produce symptoms of themselves. Dickson[2] takes a rational view in considering congenital defects "important in that they cause weakness in the spinal architecture, thus providing points of lowered resistance to strain and rendering the spine more vulnerable to injury." The author[5] in a series of 100 consecutive cases of back strain found abnormally placed articular facets in 63 per cent of the series—too high a percentage to ignore. Certainly a spine is potentially mechanically weak whose postero-lateral articulations are not the same on right and left sides. When the laminæ of the fifth lumbar or first sacral segments fail to fuse, the erector spinæ muscles have a fibrous origin instead of a bony origin and the region is more vulnerable. Spina bifida occulta presents a similar but more vulnerable area. Unilateral sacralization is frequently a cause of pain especially when arthritic changes obtain in the adventitious joint between the sacrum and transverse process. Butterfly transverse processes on the fifth lumbar also predispose to strain and may even produce a list. Bilateral sacralization gives apparent strength to the fifth but really forces the normal range of flexion at the lumbo-sacral joints onto those of the fourth lumbar, and so pre-disposes to strain. Combinations of these defects certainly increase the vulnerability of the back.

Intervertebral Disc Changes.—Due to improved x-ray technic, and the work of Schmorl in Dresden, the intervertebral disc is becoming recognized in spinal disease. Many variations in the discs do occur, but the concensus of opinion seems to be that most of the changes seen in x-rays of the discs are without clinical significance. Williams[13] has shown that disease in the disc between the fifth lumbar and the sacrum may lead to loss of the disc with narrowing of the intervertebral foramen and sciatica. Lumbo-sacral facetectomy was necessary to relieve the pain in his cases. Schmorl's bodies, or herniation of the discs into the vertebral bodies, are probably of no clinical significance, but occasionally the annulous fibrosus may rupture posteriorly and allow prolapse of the nucleus pulposus into the neural canal as found by Mixter and Barr[12] in nineteen cases at operation. Such cases present true neurological findings, however, and must be rare.

Accidental Injuries.—Traumatic injuries to the lower back seem to be increasingly common. The simple contusions, tears of lumbo-dorsal fascia, and partial ruptures of muscles, are usually easily diagnosed from the history of accident and the physical signs. The tenderness in these injuries is quite superficial and sharply localized—constantly in the same spot. There may be muscle spasm in these injuries, and it is important to remember that the pain of muscle spasm is referred to the area of the muscle group and not to the point of injury. Muscle spasm is limited to a muscle group and is usually present during rest as well as during action; moreover, the spastic muscle is tender even at rest, and the contracted muscle bundle is usually palpable. Voluntary muscle contraction involves a larger group of muscles, and while it may be protective, it may also be exaggeration.

Sprains.—The severer injuries, involving the ligaments, are more perplexing because of the necessity for differential diagnosis between lumbo-sacral and sacro-iliac lesions. In some cases both are involved, and the history and subjective complaints do not help in differentia-

tion. Both lumbo-sacral and sacro-iliac lesions may present a list, muscle spasm, limited motion, and tender points. In general, sacro-iliac cases present less limitation of spinal flexion when seated, and lumbo-sacral cases are negative to the crest-compression test. As Key[8] has pointed out, "the most important differential point is the localization of the acute tenderness. In lumbo-sacral strains this is just above and mesial to the posterior superior iliac spine on the side of the lesion, and in sacro-iliac cases the tenderness is most acute over the posterior inferior spine and sacro-sciatic notch." Sacro-iliac strains are rare in men. The recent paper by Brahdy is the clearest explanation of these physical signs that has appeared to date, and is worth careful study.

Isolated Fractures.—Mitchell[11] has drawn attention to fractures of the articular processes of the lumbar vertebræ with the interesting observation that such fractures show a strong tendency to non-union. Fractures of the spinous processes are usually due to direct violence, and sometimes they do not unite and may require excision if troublesome. Fractures of transverse processes may be due to direct or indirect violence, and those of the second, third, and fourth lumbars are the most susceptible to fracture. These fractures are characterized by point-tenderness over the fracture, and pain on hyper-extension of the thigh, or flexion of the thigh against resistance. Fractures of the pedicles and laminæ are rare and are usually due to direct violence or twisting forces. They are difficult to diagnose with certainty except when associated cord signs warrant open operation. Compression fractures of vertebral bodies occur usually in the dorso-lumbar region, but occasionally the lower lumbars are also fractured. Marginal fractures of the bodies also occur, but these should offer no particular difficulty in diagnosis. One should never be satisfied with mediocre x-rays of this region; good, clear fine-focus work is necessary to determine whether a compression fracture is recent or old—and sometimes this important distinction saves much embarrassment in court later on.

Spondylolisthesis.—Forward displacement of the fifth lumbar on the sacrum may be due to congenital anomalies, or it may be traumatic as the author pointed out years ago.[4] The difficulty with this condition lies in the determination of whether injury caused the displacement, or aggravated a pre-existing condition. Meyerding[9] considered spondylolisthesis traumatic in about 40 per cent of his cases. So far as I know, no one has ever reduced, or replaced, a spondylolisthesis. The condition must be fused where it is to gain permanent relief.

Sciatica.—This term signifies a painful condition along the sciatic nerve. Except in those rare cases of real sciatic neuritis which present the reliable signs of atrophy in thigh and calf, sciatica is usually a symptom—not of nerve trunk tenderness, but of hamstring spasm or pyriformis muscle irritation as Freiberg[3] has shown. Perhaps the commonest cause of such irritation is sacro-iliac arthritis, but nearly any of the conditions enumerated above may produce it.

Treatment

A correct diagnosis is necessarily essential to proper and successful treatment of low back pain, but the prognosis depends largely upon whether a normal spine is involved. Injuries to normal spines heal in the same way as injuries to other parts of the body, but require a longer healing period because of the difficulty in fixation and securing absolute rest. Injuries to abnormal spines require a much longer healing period; and "may never return to their former condition capable of functioning under ordinary circumstances" according to Dickson.

In general, the acute cases require rest in bed—usually absolute and continuous rest so long as muscle spasm persists. During this period applications of hot, wet packs, or dry heat, hasten the healing process. Frequently adhesive strapping steadies the back and gives much comfort. Diathermia, especially the new short-wave type, is of great value in relieving pain in acute cases, but only when it is readily accessible. The various therapeutic lamps have no particular superiority over wet and hot packs—in spite of the claims made for them which border on quackery.

The severer cases with isolated fractures, a list, or deformity, sometimes require manipulation under anesthesia, followed by absolute immobilization in a close-fitting plaster of Paris jacket. These jackets are best applied in slight hyper-extension to relax the muscles; they should be molded well in over the iliac crests in order to securely grasp the pelvis. Usually the plaster jacket is supplanted by a brace as the condition

improves. The Osgood type of brace with its butterfly pelvic girdle and axillary-crutch support offers the best immobilization but must be made from a plaster cast. The Goldthwait, or Boston back brace offers good support to the lower back and is not so cumbersome to wear. One must not overlook the dangers of too long a period of immobilization when employing jackets and braces. The patient may become too dependent upon this support, and too prolonged immobilization may lead to stiffening of the spine or aggravation of spondylitis. Braces should be discarded gradually and graduated exercises should be taken during this period with gentle massage. Too early resumption of full function is also to be avoided and it is well to caution the patient against bending, stooping, lifting and long automobile rides on his return to activity.

Patients with injury superimposed on congenital abnormalities, spondylolisthesis, and isolated fractures may fail to respond to such routine therapeutic measures as outlined above. Such cases require fusion operation. The simplified technic of spinal fusion which I have reported[6] is practically free from shock and offers almost certain fusion if carefully performed. Fusion is to be reserved, of course, for special cases, and those which recur after recovery. Postponement of definitely indicated operative treatment only prolongs the healing period and increases the disability.

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CASE REPORTS

INTESTINAL OBSTRUCTION COMPLICATING TWIN PREGNANCY*

ROBERT E. PRIEST, M.D.

Worthington, Minnesota

Intestinal obstruction during the course of pregnancy occurs rarely. Cases are reported in medical literature from a variety of causes. Drew-Smythe's case was due to pressure of a hydrocephalic head on the colon at the brim of the pelvis.[5] Adhesion of the hepatic flexure of the colon to a gangrenous gallbladder during pregnancy is reported by Beasley.[2] Ridler[6] found volvulus of the pelvic colon which he relieved and his patient delivered uneventfully, four week later. J. Whitridge Williams,[7] in the 1930 edition of his "Obstetrics," stated that he had seen but two cases of intestinal obstruction complicating pregnancy. One of these was due to intussusception at the site of a tuberculous ulcer, and the second to constriction of the bowel by a peritoneal adhesion following tuberculous peritonitis. Another case resulting from adhesions is that of Burke-Gaffney,[4] whose patient had previously suffered a ruptured appendix with peritonitis, and later an operation for cholelithiasis and freeing of adhesions. Battman and Imerman[1] report a case of obstruction due to gangrenous bowel found when operation was done with a preoperative diagnosis of empyema of the gallbladder. This serves to illustrate the variation in causes of intestinal obstruction during pregnancy, and is not an attempt to survey the literature on the subject.

Because of the unusual nature of the obstructing lesion, and because of the diagnostic difficulties in-

*From the Worthington Clinic

volved, a review of my case with necropsy findings is given here.

Report of Case

Mrs. M., aged twenty-nine years, came to the clinic for prenatal care, March 8, 1935, having menstruated last on December 15, 1934. She had been delivered of twins three years previously at her first pregnancy, and she was then pregnant for the second time. At this examination the abdomen was normal to palpation and the uterus could be felt just above the symphysis. The patient said that she felt very well. Urinalysis was normal and the blood pressure was 124/70. General physical examination was negative.

The patient was seen again May 6, 1935, when she complained of dull pain in the left side of her abdomen at the level of the umbilicus. The pain was worse on lying down and had been present for one week. At this examination, blood pressure was 120/70, temperature 99° F., and pulse 84. A nodular mass, estimated at 6x6x4 cm., was palpated in the left upper quadrant of the abdomen at the upper left border of the pregnant uterus. It was not tender and was thought by a consultant to be ovarian. The possibilities of uterine fibroids and a tumor of the colon were also considered. The patient was instructed to return in one week.

Ten days later, on May 16, the patient called at my office to say that while she was seated at breakfast that morning she had a sudden sensation of diarrhea, and upon investigation found that she was passing bright red blood by rectum. Because of the abdominal mass previously discovered, and this history of rectal bleeding, a tentative diagnosis of tumor of the large bowel was made, and a barium enema was done. This was unsatisfactory on the first trial when the patient expelled the barium because of discomfort before the film could be exposed. The second attempt was more successful, and the colon appeared to fill normally although perfect visualization was impossible because of the pregnant uterus.

A proctoscopic examination was done May 20, and the mucosa of the rectosigmoid appeared normal except for a small bleeding ulcer on the anterior wall, 8 or 10 cm. above the anus. This ulcer was cauterized with 50 per cent silver nitrate.

The patient was admitted to the hospital June 21 because of extreme nausea and moderate intestinal cramps. No food was given by mouth, and large quantities of intravenous glucose in normal saline were given. Temperature and pulse were well within normal range throughout the hospital stay, and the patient's nausea and pain were much improved, though never entirely relieved. Soft foods and liquids were tolerated. The nodular mass, previously palpated, was still present and no change in it could be detected. By palpation it was thought that two fetal heads were present, but only one fetal heart could be located. A diagnosis of twin pregnancy was made by roentgenogram. The patient was discharged from the hospital on June 24, at 4:00 p. m.

At 10:00 p. m. of that day, labor began, and at 11:30 p. m. the patient was readmitted to the hospital. Labor progressed very rapidly, and the first twin (OLA), a boy, was born at 12:35 a. m. The second twin, a girl, presented by the face, and was delivered by internal podalic version and breech extraction at 12:50 a. m. There was profuse bleeding after expression of the placenta, but it was controlled quickly by pituitrin and ergot. The patient's condition on recovering from the anesthetic was good, and continued to be so except for an elevated pulse rate, until 8:00 p. m. the following evening, when she had emesis of 200 c.c. of undigested food, and complained of intense, crampy pain in her abdomen. Hot turpentine stupes were put to the abdomen, and the pain was controlled by codeine. A large enema, given at this time, returned with formed stool. The patient had a fairly comfortable night, but the next day she was quite distended.

Continuous duodenal suction through a nasal catheter was begun during the evening of the second postpartum day, and the patient was very much relieved. The abdomen became much less tense, but never scaphoid. The suction tube was left in place for one week, during which time the patient received two whole blood transfusions of 500 c.c. each, and 2,000 c.c. daily of 10 per cent glucose in normal saline, intravenously. Turpentine stupes were continued and pituitrin injections given several times daily. The distended bowel gradually resumed its tone and the patient began to pass flatus freely, with some liquid stool. The temperature had always been normal, and the pulse, which had been elevated, returned to a normal rate. The patient took soft food by mouth and when the duodenal tube had been clamped for twenty-four hours during which time there was but one small emesis, the tube was removed. The patient immediately became distressed, pulse rose to 120, and in five hours the duodenal tube was reinserted because of extreme abdominal distention with intermittent, crampy pain. The tube did not give relief this time, and the distention continued. The temperature was 102° F. (oral) at this time. This was the first time since admission that temperature was above 99° F.

Because the symptoms of obstruction had recurred so promptly upon removal of the duodenal tube, and because of the abdominal tumor and its antecedent history, it was thought that the obstruction was undoubtedly mechanical in nature, and that surgical intervention was needed. The patient was referred to Dr. C. F. Dixon of the Mayo Clinic, and it is through his courtesy that the remainder of this case history is presented. The trip to the Mayo Clinic was uneventful, and, on arrival, duodenal suction gave relief of distention. Pulse rate on admission was 134 and temperature, 97° F. The patient was transfused twice, and general supportive treatment given. She was quite comfortable until shortly before her death, which occurred two days later. Her highest temperature reading was 102.4° F. and her pulse rate, just before death, was 160.

A summary of the autopsy report is as follows: perforating carcinoma of the sigmoid, inoperable, with generalized peritonitis and metastases to the aortic lymph nodes. The growth appeared to have been present for many months.

Comment

A case history is presented of a young woman pregnant with twins who died of inoperable carcinoma of the bowel slightly less than two months after the appearance of her first symptoms relating to the tumor. Because the enlarged uterus made palpation of the exact connections of the tumor impossible, and because proctoscopic examination of the rectosigmoid showed seemingly normal mucosa, it was felt that interruption of the pregnancy was not justified.

The diagnosis of colon tumor would doubtless have been made much sooner if the patient had not been pregnant. It is doubtful if the outcome would have been changed because death occurred less than two months after symptoms appeared and, judging from the appearance of the tumor, it must have been present for many months. It is well known that symptoms do not appear early in the life of these tumors

since they produce little stenosis due to the wide lumen of the colon.[8]

The babies were delivered about six weeks before term. Each weighed less than five pounds and was unable to swallow or suckle sufficiently to nourish itself at birth. They were tube-fed for three weeks and at the time this is written are four months old and doing very well.

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TWIN INTERSTITIAL PREGNANCY*

PETER E. HERMANSON, M.D.

Hendricks, Minnesota

INTERSTITIAL pregnancy is a rather rare complication, occurring less frequently than in other portions of the tube. The etiology of such a condition is not definitely known, although inflammatory changes in the tubes are felt to play a definite part. Interstitial pregnancy almost always results in rupture, and early surgical treatment is imperative.

Glaesmer of Berlin classified interstitial pregnancy into three types, according to the direction in which the ovum develops: (1) growth in the direction of the isthmus; (2) growth in the musculature of the fundus uteri; (3) growth in the lateral wall of the uterus.

Diagnosis is very difficult. Signs which may be present are: (1) a wide base of the uterus and displacement of the round ligament; (2) an oblique upper boundary of the uterus (Simon-Ruge sign) due to the hypertrophy of one of its angles; (3) hemorrhage.

Case Report.—Mrs. M. S., aged twenty-three, had been married three years, but had never been pregnant previous to the time of entrance to the hospital. She was brought into our hospital at 4:00 p. m., October 28, 1935, in collapse, very pale and with definite evidence of an internal abdominal hemorrhage. She had always been well and had had no serious illnesses other than the usual childhood diseases. The menses had begun at the age of fifteen and had always been irregular, sometimes being absent for as long as three months. The last period had begun on July 4.

The young woman had felt very well until October 19, when she became suddenly ill and went to bed. She felt better that evening and went out, but became nauseated and vomited and had some abdominal pain. She then went to bed and remained there the rest of the week. Her weakness continued and toward the latter part of the week she began to develop some distention of the abdomen. There was no vaginal bleeding at any time during her illness. On October 28, the family physician was called and she was brought to our hospital, arriving about 4:00 p. m.

When first seen, the patient was gasping for air and her mucous membranes were extremely anemic. Dehydration was present and she presented the general picture of an internal hemorrhage. The heart was very rapid but the lungs were clear. The abdomen was distended and very tender over the lower portion. On admission, the temperature was 99.6, the pulse 120 and thready, and the respiration twenty-four.

The blood picture showed: Hemoglobin (Dare), 10 per cent; red blood cell count, 1,290,000; white blood cell count, 50,500; differential—polymorphonuclears 96 per cent, small lymphocytes 5 per cent, eosinophiles 1 per cent, several nucleated red blood cells. A catheterized specimen of urine showed: sugar—none; albumin—trace; numerous hyaline and fine granular casts.

Three relatives who were with the patient were grouped but no satisfactory donor could be obtained at that time. The patient was given intravenous glucose, 10 per cent in distilled water, but died at 10:00 p. m., October 28.

Permission to do an abdominal postmortem was granted. The abdomen was opened and found filled with blood. Two fetuses of approximately three months' gestation were found, floating among the coils of intestines. At the upper right quadrant of the uterus, in the region of the interstitial portion of the tube, there was a perforation which was large enough to admit a finger easily. The placenta was free in the abdominal cavity as well as the membranes, although some membrane was still adherent to the opening in the upper right quadrant of the uterus. The tubes and ovaries were normal, and the stomach, intestines, liver, gallbladder and appendix were all normal except for an extreme anemia evident in all of these organs.

W. W. Will, M.D.
President, Minnesota State Medical Association

President's Letter

TIME was when the duties of the president of the Minnesota State Medical Association consisted mainly of membership on many commissions and committees of which he never attended a meeting, of presiding over the annual meeting of the House of Delegates and delivering a long and eloquent address at the banquet afterwards.

Those were the days when medical men were banded together chiefly for scientific advancement and the presidency was simply an award of professional distinction.

Those days are past. The president of 1936 is confronted with real tasks and real responsibilities.

Today it is not merely a question of maintaining scientific standards but of defending the very citadel of individual freedom and personal rights in the United States.

Once the socialization of medicine was a purely academic question. Now it is regarded by too many active propagandists as a practical possibility for legislation at this Congress, or the next.

The social and economic implications for the entire population cannot be overestimated. Upon the physician, first and foremost, now rests the burden of defense of the rights of the individual.

I am humbly aware of the honor done me as president of the Minnesota State Medical Association in these critical times. I am also acutely aware of the difficulties and the responsibilities that lie ahead and grateful that there is a distinguished, wise, and active group of officers, committee members and councilors in Minnesota to advise and assist me at every step.

These men have proved their unselfish devotion to the profession of medicine over many years. But in these difficult times it is not enough for the officers to devote themselves to our work. We shall not survive the social upheavals of the times unless every single member is aware of our responsibilities and our problems.

Today, I ask the coöperation and assistance, not only of my colleagues on the Council, but of every single member of the Association.

We as physicians and professional men are dedicated in a very special sense to the public welfare. We must choose our course well. If, then, we maintain a united front, neither direct attack nor subtle propaganda, will prevail against us.

W. W. WILL.

EDITORIAL

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BUSINESS MANAGER
J. R. BRUCE, Saint Paul

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Retrospect and Prospect

With the advent of a new year we are prompted to reflect on the occurrences of the past year and to look forward to activities in the year 1936.

One of the outstanding losses which the past year brought to the Association was the passing of Dr. Herman Johnson, for so many years chairman of our Legislative Committee. His unselfish devotion and outstanding ability in presenting the views of the profession to the legislature and in obtaining action will be greatly missed. Dr. L. L. Sogge, who has been very active in Association affairs, has consented to carry on as chairman of the Legislative Committee and deserves the united support of members of the profession. Dr. Johnson's successor as delegate to the American Medical Association will be elected by the House of Delegates of the State Association at their next meeting, which will be held just prior to the meeting of the American Medical Association.

Our last annual meeting, held in Minneapolis in June in conjunction with the Medical Section of the American Association for the Advancement of Science, had an all time record attendance. Our 1936 meeting will be held in Rochester, May 3 to 6, inclusive. Last year some sixteen guest speakers from outside the state made up most of the scientific program, an innovation which will not be continued this year, as members of the Association will provide the bulk of the scientific program. Clinics at St. Mary's Hospital will constitute the early morning program each day at the Rochester meeting. The program committee, consisting of the chairmen and secretaries of the Medical and Surgical Sections, is as follows: Medical Section—Dr. Frank J. Hirschboeck, chairman, and Dr. Charles N. Hensel, secretary; Surgical Section—Dr. Gordon B. New, chairman, and Dr. Theodore H. Sweetser, secretary. The committee has lined up the scientific program and already more exhibit space has been sold than at the last Rochester meeting.

The State Association will be led this year by Dr. W. W. Will of Bertha. Born in Blue Earth County, trained medically at our University Medical School and a practitioner at Bertha for thirty years, Dr. Will is a Minnesota product. Having been a past president of both the Upper Mississippi Medical Society and the Northern Minnesota Medical Association and for some twelve years a Councilor for the Seventh District of the Minnesota State Medical Association, Dr. Will is well prepared to perform the duties of his new office.

The Mayo Clinic and the profession of the state and nation sustained an irreparable loss in the death of Dr. E. Starr Judd, the surgeon, and Dr. George E. Brown, the internist, who died only a day apart. Dr. Judd had endeared himself to members of the profession generally through his unassuming personality and his ability as a surgeon. He possessed not only remarkable surgical technic, undoubtedly fostered by an immense experience, but in addition sound surgical judgment—two assets of a real surgeon. Dr. Brown, in the less spectacular field of internal medicine, had also made his name known na-

tionally through his work on vascular diseases when he was cut down in his prime. The places of both these men will be hard to fill.

At the University of Minnesota two outstanding changes in personnel deserve mention. Dr. Richard E. Scammon, who had been Dean of Medical Sciences at the Medical School since his return from the University of Chicago several years ago, was honored with a distinguished service professorship. This appointment relieves him of burdensome administrative duties, enabling him to devote his time to scientific investigation. Dr. Harold Diehl, whose industry has been responsible for the building up and efficient operation of the Students' Health Service since 1921, was at the same time appointed Dean of Medical Sciences. He retains his title of Director of the Students' Health Service with Dr. Ruth Boynton as Acting Director.

With the socialistic trends in American life reflected in the state and federal government, there is need as never before for medical organization and concerted action. Innovations in the supplying of medical care should be carefully weighed before time honored methods are put into the discard.

Edward Starr Judd

The sad news of the death of Starr Judd on November 29 came as a shock to his many friends and admirers in the profession.

We like to think that the career of Starr Judd typifies the high plane of medicine in Minnesota. Born in Rochester, Minnesota, and educated medically at the University of Minnesota, this brilliant member of our profession developed with the Mayo Clinic. The large amount of surgical work he was privileged to perform since he, as a mere youngster, became head of a surgical section at the Clinic in 1904 served to develop a natural dexterity and at the same time a surgical judgment, both unsurpassed. Those who came from near and far to attend his clinic said he never made an unnecessary or false move.

Interested in organized medicine, Dr. Judd was president of the Minnesota State Medical Association in 1923. He also served as secretary of the section on surgery of the American Medical Association (1913-1916), chairman of the section (1917-1918), second vice president (1918), and president (1931-1932).

In spite of his many activities, his contributions to medical literature numbered over three hundred and he wrote and spoke with authority.

It was Starr Judd's character, however, that endeared him to all with whom he came in contact. Unassuming and kindly, he never held himself aloof but seemed to meet people on their own plane. Many will miss him with deep regret.

OF GENERAL INTEREST

Dr. Harvey J. Brekke, who has been practicing in Stillwater for several years, has moved to Minneapolis.

* * *

Dr. Max H. Hoffman, who has been associated with Dr. Arnold Schwyzer for several years, with offices at 123 West Seventh Street, St. Paul, has opened offices at 1232 Lowry Medical Arts Building, Saint Paul, where he will continue the practice of internal medicine.

* * *

Dr. Gilbert J. Leonard has been appointed by the State Board of Control as house physician at the State Hospital for the Insane at Hastings, Minnesota. Dr. Leonard graduated from the University of Minnesota medical school in 1926 and has been practicing in Saint Paul since that time.

* * *

Dr. Myron O. Henry of Minneapolis and Dr. J. C. Swanson of Fargo held an orthopedic clinic in Minot, North Dakota, on December 11 for the Crippled Children's Committee of the Elks Club. A large group of patients were examined and recommendations were made for further treatment which will be carried out by the Elks Club.

* * *

A group of physicians from New Ulm and vicinity were addressed last month at the Union Hospital by Dr. Henry E. Michelson, Professor of Dermatology at the University of Minnesota Medical School, who spoke on "Skin Diseases of General Practice," and by Dr. Leo G. Rigler, Professor of Roentgenology, on "Diagnosis of Tuberculous Disease of the Chest."

* * *

The American Board of Ophthalmology will conduct its next examination at Kansas City, May 11, 1936, at the time of the American Medical Association meeting and in New York City at the time of the meeting of the American Academy of Ophthalmology. Applications must be filed at least sixty days in advance of the examination. Forms may be obtained from Dr. Thomas D. Allen, Assistant Secretary, 122 South Michigan Avenue, Chicago, Illinois.

* * *

The eleventh revision of the Pharmacopœia was available December 16, 1935. It will become official

June 1, 1936. The Board of Trustees has decided upon "interim revisions" when indicated. The U.S.P. has served as the foundation of rational therapeutics since the first edition appeared in 1820. As has happened with each revision, the latest volume includes a number of new remedies and some minor changes in those previously included. A "Mild Tincture of Iodine" containing 2 per cent iodine and 2.3 per cent sodium iodide (instead of potassium iodide) is one outstanding change in this last revision.

* * *

The Worthington Clinic celebrated its Fifteenth Anniversary on December 10, 1935, with a banquet at the Thompson Hotel. Those present consisted of members of the staff with their families as well as office employes, nurses from the clinic hospital, and wives of deceased clinic members. There were forty-one persons present. The banquet was followed by musical numbers and addresses.

The Worthington Clinic was organized in the fall of 1920 by Drs. F. G. Watson, F. W. Metcalf, J. T. Smallwood, C. R. Stanley, and B. O. Mork, Sr. Drs. Metcalf, Watson and Smallwood have since died and their places are now filled by Drs. P. W. Harrison, B. O. Mork, Jr., and R. E. Priest.

* * *

The Radiological Review and Chicago Medical Recorder, published at Quincy, Illinois, since 1924, will change its name beginning in January and become the *Radiologic Review and Mississippi Valley Medical Journal,* the official publication of the recently formed Mississippi Valley Medical Society. The editorial policies will be the same as the old *Radiological Review* with the addition of the publication of the papers read before the Mississippi Valley Medical Society. Dr. Harold Swanberg, secretary-treasurer of the Mississippi Valley Medical Society and editor of the old journal, will remain as editor. The Editorial Board of the *Radiologic Review* will be supplemented by an Editorial Board from the membership of the Mississippi Valley Medical Society. The new publication will be published by the Radiologic Review Publishing Company, at Quincy, Illinois.

* * *

Chicago's New Fracture Ordinance

The City of Chicago recently passed the following ordinance designed to prevent as much as possible further injury to the victims of accidents often occurring during transportation to a hospital:

AN ORDINANCE

Amending Article VI (ambulances) of Chapter 45 of the Revised Chicago Code of 1931 and providing for the equipment of ambulances with first aid and splint appliances.

Be it Ordained by the City Council of the City of Chicago:

Section 1. That article VI of chapter 45 of the Revised Chicago Code of 1931 be and the same is hereby amended by inserting, between sections 2343 and 2344 thereof, a new section to be known as section 2343-a, which new section shall read as follows:

2343-a. Attendant—splints required. No person, firm or corporation shall operate or cause to be operated any ambulance, public or private, or any other vehicle commonly used for the transportation or conveyance of the sick or injured, without having such vehicle equipped with a set of simple first aid and splint appliances approved by the board of health and having in attendance at all times such vehicle is in use a person who has obtained a certificate of fitness as an ambulance attendant from the board of health.

Any person desiring a certificate as an ambulance attendant shall make application in writing therefor to the board of health. Before the issuance of any such certificate the applicant therefor must present evidence of his qualifications to fill such position and must demonstrate to the satisfaction of the board of health his ability to render emergency first aid and to apply approved splints to arm and leg fractures.

Section 2. This ordinance shall take effect and be in force from and after its passage and due publication.

The *Chicago Tribune,* in commenting on this ordinance in its issue of November 5, 1935, says:

"By bundling a traffic victim into the first available automobile and rushing him off to a hospital without adequate first aid care, the good Samaritan often does more harm than good. Serious harm is often done by the kindhearted passing motorist who picks up the victim, doubles him up to get him through the narrow door of his car, twisting the dangling broken leg or arm and increasing the peril to the unfortunate victim."

CAPROKOL OMITTED FROM N. N. R.

The Council on Pharmacy and Chemistry reports that Caprokol (Hexylresorcinol-S. & D.) was accepted for inclusion in New and Non-official Remedies, 1924. The following dosage forms were accepted by the Council: Capsules Caprokol (Hexylresorcinol-S. & D.), 0.15 Gm.; Caprokol (Hexylresorcinol-S. & D.), 2½ per cent Solution in Olive Oil; Hexylresorcinol Solution S. T. 37. When the customary three year acceptance period expired in 1931, the Council voted to reaccept Caprokol provided the manufacturers agreed to make a drastic revision in their advertising propaganda and to submit convincing evidence of the therapeutic value of the drug in all the numerous conditions in the treatment of which its use was recommended. In the couruse of the next two years the firm omitted a number of the most objectionable circulars and submitted evidence on the question of the analgesic action. At the time that Hexylresorcinol Solution S. T. 37 was omitted from New and Non-official Remedies because of the firm's refusal to comply with the rules of the Council, the firm requested omission of Caprokol also, stating that its continued inclusion after the exclusion of Hexylresorcinol Solution S. T. 37 might prove a source of misunderstanding with the Council. Meanwhile the firm had not submitted the new evidence required to substantiate the claims made for the product as a germicide and as a genito-urinary antiseptic. As a result of these considerations, the Council voted to omit Caprokol because the claims for its therapeutic value have not been substantiated and because the manufacturer finds it impossible to handle this substance and certain of its dosage forms separately from the unacceptable dosage form, Hexylresorcinol Solution S. T. 37. (J. A. M. A., May 25, 1935, p. 1909.)

MEDICAL ECONOMICS

What Can I Do For My County And State Medical Society?

Suggestion Number Four

1. Read the communication from Dr. B. J. Branton on the malpractice situation and Medico-Legal Advisory Committee printed in these columns.

2. Discuss your local situation and see that every member understands the new plans of this committee and also how to take advantage of the assistance offered by this new medical agency.

3. Impress upon your fellow members the fact that no new machinery for the handling of malpractice litigation difficulties will be successful without the coöperation and careful watchfulness of his conduct by each individual member.

It is thanks, largely, to the interest and careful preparatory study of Dr. Branton that the Minnesota State Medical Association is now ready to take this hopeful new step toward adjustment of its malpractice problems. The obligation of the membership to do its share in righting matters goes without saying.

Have you studied the present situation and prospects for the immediate future of care of the indigent in your county, according to last month's suggestion?

Remember that official arrangements made now for medical care of the sick poor are likely to have a permanent character.

It is the special obligation of the physician to see that the public welfare and the welfare of the medical profession are served. Write to the State Office for information or assistance if you plan to take this matter up officially with your county or township authorities.

Medico-Legal Advisory Committee Meets

One of the most important developments of the year in medico-legal matters is the appointment and prompt marshalling for action of the new Medico-Legal Committee.

This committee, originally called the Legal Defense Committee, was appointed at the direction of the House of Delegates and the Council and at the suggestion of Dr. B. J. Branton of Willmar, member of the Committee on Medical Economics.

It has already held two meetings and provided a practical plan for securing prompt information about every threat of malpractice action against a member of the association.

The plan provides for a special card to be sent out to each member with his membership card at the time he pays his dues.

This card is to be signed and returned to the committee at once in case of threatened action. The committee will then send blanks to be filled out with pertinent information and advise the member,

Malpractice Rates Increasing

Malpractice suits are increasing. Rates for protection are going up. Insurance companies will shortly refuse to write malpractice insurance at any feasible premium rate unless some action is taken to improve the malpractice situation.

Dr. Branton, who has made a thorough study of the subject, is chairman of the new committee, which includes also Dr. W. H. Hengstler of St. Paul and Dr. W. L. Burnap of Fergus Falls.

The communication by Dr. Branton printed below is of special interest and importance. It will be followed by others to be printed in future issues in these columns.

"To Guard Material Interests"

"Fitting in as an integral part in the work of the Economics Committee of our state association, the newly organized Medico-Legal Advisory Committee at its first meeting adopted certain measures of great importance to the members of the Minnesota State Medical Association.

"From Article 11 in the Association's Constitution they took the following as the basis for its existence and future work. 'To guard and foster the material interest of its members and to protect them against imposition.'

"The fact that there are more than 4,000 malpractice suits brought against doctors in the United States each year, that these suits are encouraged, many times unknowingly, by men in our own ranks in Minnesota, thereby causing a marked increase both in number of cases and size of premiums members must pay insurance companies for protection, made the committee fully cognizant of the magnitude of the problem they are facing.

"Remember, You May be Next"

"Therefore, they must ask for the full coöperation of every member in good standing that records may be filled out as requested from time to time, letters answered promptly and an unselfish reversion to the standards of 'Do unto others as you would have others do unto you' strenuously adhered to in each community. Remember, always, that unwise actions by you and destructive criticism when consulted by former patients of another, while pleasing to the patient who is looking for a chance to sue your neighbor, can revert back to you. *You may be next.*

"The card which each member will receive the first of January when he pays his dues should be kept guarded and handy. Your committee, of course, hopes you will not need to use it during 1936, but remember that they stand ready to give you the best advice obtainable when you are in need of it.

"Yours the 'ounce of prevention,' the committee's the 'pound of cure.'"

Debates—Early Returns

When the University of Minnesota debated the University of Iowa early in December on the subject—

> Resolved: That the several states should enact Legislation providing for a system of complete medical service available to all citizens at public expense—

Minnesota, on the affirmative side, won.

It is heartening to know, however, that for one victory for the Affirmative there have been a half a dozen defeats among the college debating teams.

In the *large majority* of debates, here and in other states, the negative has carried off the victory.

High school debaters have been listening with interest to these debates and getting pointers from them for their own contests which will be in full swing during January and February. Winning teams will be arguing for the regional and state championships in March and April.

Helping the High Schools

There is still time to assist the high school teams. Members should not fail to look up the list printed in the December issue to see if any schools in their own communities have entered the debate.

The Minnesota Debate Handbook prepared by the Minnesota State Medical Association is off the press and can be secured at the State Office, 11 W. Summit Ave., St. Paul, together with other material that is not otherwise available to the debaters.

Printed arguments are not enough, however, and arrangements should be made in every case for friendly personal discussions with the debaters.

Society representatives will have a unique opportunity for presenting the attitude of organized medicine to the question of compulsory medical care following the public debates and pending the judges' decision. Arrangements must be made in advance.

"Credit Plans"

The question of collections always presents difficulties to the physician.

"Fly-by-night" collection agencies have traded lucratively and knavishly upon these difficulties.

It should be remembered by all physicians who are solicited by unfamiliar agencies, that the up-to-date entrepreneur no longer presents himself as a "collection agent."

He has been reading the medical magazines, and he knows that new plans for extension of medical credit are in the air. He presents a "credit plan" which is going to solve all the physician's difficulties, put "low-income" patients on a long-time payment plan, put real money into the hands of the doctor and at the same time make the patient happy, independent and solvent.

The principles involved may be very good. But the proponent will bear the same investigation as the old fashioned credit agency.

When any such plan is presented to you be

sure to check up on the agency with the Corporation Department of the office of the Secretary of State at the State Capitol in St. Paul. Also write to the State Medical Association office for whatever information may be on file with the secretary of the association.

Abuse of Free Service Studied

A recent analysis of free medical service and its abuse in six out-patient clinics in Chicago yielded the following result:

Out of 1,043 cases that were completely studied, 136 or 13 per cent were found to be cases of frank abuse.

In one of the six clinics studied the rate was found to be consistently high: an average of 22 per cent of the cases treated being instances of abuse.

In others the rate was consistently much lower than 13 per cent.

The institutions with the highest standards, the best qualified medical social service staff, the most efficient and satisfactory standards in admitting and routing patients showed the fewest cases of abuse.

Need for more thorough medical social service work to investigate home conditions, not only with reference to ability to pay, but as an aid to effective medical care, was apparent.

Need, also, for formulating principles and standards for admittance, for the number of patients to be handled and for general efficiency in handling them was emphasized.

The study was made by Dr. William Henry Walsh, director of the survey, for the Committee on Medical Economics of the Chicago Medical Society.

The committee recommended that the Society employ a special medical social service worker of its own whose duty. it would be to assist the out-patient clinics in the work of selecting proper patients for free service and in the improvement of that service.

Survey Sidelight

Interesting side-light on the progress of the "Doorbell Health Survey":

Supervisors have been congratulating themselves on the high caliber of enumerators secured among "white collar workers" on the relief rolls, to make the survey.

They cited one man particularly to a group of Minnesota physicians. This man had been educated in medicine in Vienna but never licensed to practice in the United States.

Shades of all the great quack vendors!

The State Secretary promptly unearthed the fact that the wife of this unusual enumerator has already been prosecuted and sentenced for irregular practice in Minnesota.

With a list of the chronically ill such as the United States Public Health Service is now assembling, bright new worlds would surely open up for the fake cure men to conquer.

Medical Care Satisfactory For WPA Workers

Medical care for injured WPA workers is proceeding smoothly according to WPA officials.

Absence of complaints from physicians who have participated corroborates administration reports.

Up to December 1 a total of 259 vouchers for completed medical services to injured workers had been approved by state offices and sent on to Washington for payment.

Most of these were for minor injuries. A number of injuries of a major nature that were incurred before December are still under treatment and completed vouchers have not yet been sent to Washington.

Approximately 55,000 workers, Minnesota's entire quota, were under employment on WPA projects as this issue went to press. That means that the number of injured workers will increase rapidly in the next few months.

Medical men in the vicinities of WPA projects have been participating with marked fairness in this work.

Each district supervisor has a list, provided through the State Office, of physicians in the locality who are willing to engage in the work. The patient is allowed his choice from among these physicians if he has one and if it is convenient. Otherwise he is assigned to a physician by the supervisor and the work is rotated fairly among the physicians.

No Dispensaries

In Minneapolis and St. Paul each physician on the list has received some work and, in St.

Paul, the work is now going the rounds a second time.

No central dispensary is operating in either city or Duluth under the WPA. The dispensaries that treated minor injuries and also routed patients under the CWA and under SERA work relief were not re-opened under WPA management. Patients are routed direct to physicians or hospitals from the work projects.

A few physicians are still sending their bills direct to Washington and thus slowing up payment. WPA officials re-emphasize the importance of sending bills on the regular form S-69 direct to the District Supervisor's office *and sending them promptly.*

"Increasing Agitation"

From a letter sent to selected physicians by the Debaters Information Bureau, Portland, Maine:

DEBATERS INFORMATION BUREAU

Publishers of Debate Services, Programs, Readings and "Platform News"

45a Free Street, Portland, Maine

J. Weston Walch
General Manager

Dec. 7, 1935

Dear Sir:

I don't know what you think of it, but I am sure you are tremendously interested in this increasing agitation for State Medicine.

THE ROSENWALD FUND HAS JUST APPROPRIATED A QUARTER OF A MILLION DOLLARS TO FURTHER SOCIALIZATION OF MEDICINE. THE CALIFORNIA LEGISLATIVE COMMITTEE HAS UNANIMOUSLY REPORTED IN FAVOR OF HEALTH INSURANCE; ALBERTA HAS ADOPTED IT. THIS WINTER, 100,000 BOYS AND GIRLS IN 8,000 AMERICAN HIGH SCHOOLS WILL DEBATE STATE MEDICINE BEFORE AUDIENCES TOTALLING OVER A MILLION PEOPLE!† * * * * *

†The capitals are ours.

Minnesota State Board Of Medical Examiners

List of Physicians Licensed by the Minnesota State Board of Medical Examiners on November 13, 1935

By Examination

(October Examination)

Baggenstoss, Archie Herbert, U. of Cincinnati, M.D., 1934, Rochester, Minn.

Behrend, Albert, U. of Pennsylvania, M.D., 1932, Rochester, Minn.

Boettner, Roland Buell, U. of Minn., M.B., 1934; M.D., 1935, Jersey City, N. J.

Carmichael, Francis Abbott, Jr., U. of Pennsylvania, M.D., 1934, Rochester, Minn.

Clark, Randolph Lee, Jr., Med. Coll. of Va., M.D., 1932, Rochester, Minn.

Cook, Malcolm MacDonell, Emory U., M.D., 1933, Minneapolis, Minn.

Cooper, Charles Cole, U. of Minn., M.B., 1932; M.D., 1935, St. Paul, Minn.

Famiglietti, Edward Virgil, Johns Hopkins U., M.D., 1933, Rochester, Minn.

Fisher, Isadore, U. of Minn., M.B., 1935, Duluth, Minn.

Ganshorn, John Alexander, U. of Manitoba, M.D., 1932, Rochester, Minn.

Gibson, William Roland, Stanford U., M.D., 1934, Rochester, Minn.

Ginsberg, Maurice, U. of Minn., M.B., 1935, Minneapolis, Minn.

Goldstein, Moe, U. of Minn., M.B., 1934; M.D., 1935, Rochester, Minn.

Good, Clarence Allen, Jr., Washington U., M.D., 1933, Rochester, Minn.

Gurney, Charles Ernest, U. of Nebr., M.D., 1930, Rochester, Minn.

Hamlon, John Spencer, U. of Minn., M.B., 1935, Minneapolis, Minn.

Jackman, Raymond Joseph, U. of Iowa, M.D., 1930, Rochester, Minn.

Johnsrud, Luverne, U. of Minn., M.B., 1935, Minneapolis, Minn.

Juers, Arthur Louis, U. of Louisville, M.D., 1931, Minneapolis, Minn.

Junnila, Bruno Olaf, U. of Minn., M.B., 1935, Minneapolis, Minn.

Karlstrom, Arthur Elof, U. of Minn., M.B., 1935, Minneapolis, Minn.

Katzberg, Louis William, U. of Nebr., M.D., 1932, Fergus Falls, Minn.

Kemble, John William, Jefferson, M.D., 1935, Rochester, Minn.

Kierland, Robert Richard, U. of Minn., M.B., 1932; M.D., 1933, Minneapolis, Minn.

Layne, John Anthony, U. of Minn., M.B., 1934; M.D., 1935, Minneapolis, Minn.

Lewis, Everett Bryan, U. of Pa., M.D., 1933, Rochester, Minn.

Lipscomb, William Rutledge, U. of Colo., M.D., 1932, Rochester, Minn.

Logan, George Bryan, Harvard U., M.D., 1934, Rochester, Minn.

Lord, George Alexander, Harvard U., M.D., 1934, Rochester, Minn.

Montgomery, Thomas Robert, U. of Ore., M.D., 1932, Rochester, Minn.

Morlock, Carl Grismore, U. of Western Ont., M.D., 1932, Rochester, Minn.

Muccilli, Alfred Edward, U. of Minn., M.B., 1935, Duluth, Minn.

Mullen, Simeon Anthony, U. of Minn., M.B., 1932, Wadena, Minn.

Nolan, Don Edwin, U. of Minn., M.B., 1935, Minneapolis, Minn.

Olson, Stuart Arnold, U. of Minn., M.B., 1935, Minneapolis, Minn.

Perozzi, Thelma, U. of Ore., M.D., 1933, Rochester, Minn.

Pool, Thomas Lloyd, Northwestern, M.B., 1934; M.D., 1935, Rochester, Minn.

Powell, William Nottingham, U. of Pennsylvania, M.D., 1931, Rochester, Minn.

Ray, Robert Cassleman, Northwestern, M.B., 1931; M.D., 1932, Heron Lake, Minn.

Roy, Philemon Cheverton, U. of Minn., M.B., 1935, Minneapolis, Minn.

Sether, Arthur Fridtjof, U. of Minn., M.B., 1935, Minneapolis, Minn.

Shapiro, Phillip, U. of Minn., M.B., 1935, Minneapolis, Minn.

Stemsrud, Harold Lindell, U. of Minn., M.B., 1934; M.D., 1935, Pine City, Minn.

Stevenson, Clyde Alan, U. of Wis., M.D., 1934, Rochester, Minn.

Winer, Julius Haskell, U. of Minn., M.B., 1935, Minneapolis, Minn.

Wolfram, Donald J., Indiana U., M.D., 1934, Rochester, Minn.

Yeager, Charles LeVant, Coll. of Med. Evang., M.D., 1934, Rochester, Minn.

By Reciprocity

Clement, Walter Bertram, U. of Colo., M.D., 1934, Mankato, Minn.

Henthorne, John Charles, U. of Pittsburgh, M.D., 1931, Rochester, Minn.

Roth, Frederick Daniel, Marquette U., M.D., 1933, Lewiston, Minn.

Weiss, Irving Joseph, Creighton U., M.D., 1931, Big Fork, Minn.

National Board

Ecker, Arthur David, Johns Hopkins, M.D., 1934, Rochester, Minn.

Fritz, Wallace Lawrence, U. of Minn., M.B., 1934; M.D., 1935, St. Paul, Minn.

Grimes, Burton Piper, U. of Minn., M.B., 1932; M.D., 1933, Minneapolis, Minn.

Mason, James Anders, U. of Nebr., M.D., 1932, Big Falls, Minn.

Nesselrod, Jerrold Peerman, Northwestern, M.B., 1929; M.D., 1930, Rochester, Minn.

Tweedy, Robert Bruce, Marquette, M.D., 1935, Winona, Minn.

OBITUARY

George E. Brown

1885-1935

THE life of George Elgie Brown, of Rochester, began outside of the State of Minnesota, but his professional life began within its borders. He married in Minnesota, and after a period of absence returned to live and work here for fifteen years.

Dr. Brown was born in Grand Rapids, Michigan, in 1885. In 1909 the University of Michigan bestowed on him the degree of Doctor of Medicine and throughout the two succeeding years he served as interne in the Northern Pacific Hospital at Brainerd, Minnesota. After his marriage to Irma Parker, of Brainerd, in 1911, he settled in Miles City, Montana, where he remained in practice for ten years. In these years he was not content with mere routine but he introduced certain laboratory procedures and he brought the first fluoroscope to his part of Montana. He had been liked in medical school; in practice he became a favorite of his colleagues and of his fellow citizens. He was equally at home in a ranch house or a scientific meeting; in a mackinaw or a dinner coat. While he was still established in Miles City he spent two periods of study elsewhere: five months at Harvard in 1914 and the summer of 1916 at Johns Hopkins, where he studied organic chemistry. In 1918 and 1919 he was with the Rockefeller Foundation in France.

In 1921, Dr. Brown became first assistant in a section of the Division of Medicine of The Mayo Clinic. A position on the staff of this institution gave him even better opportunity to develop his bent toward clinical investigation and to apply scientific methods in the diagnosis and practice of medicine. His progress was rapid; he advanced to associate in medicine and to headship of a section.

Dr. Brown's contributions to medical literature began in 1911. From then onward papers and monographs were produced by him and his associates in rapid succession. Reports of approximately 150 studies bear his name. In the early years of his career these contributions ranged over a wide field of internal medicine but by 1922 his interest in the little-known field of blood vascular disease was evident. His contributions to this field in the next thirteen years were, and are, of inestimable importance. His mind was seething with projects to increase knowledge of this aspect of medicine. Fortunately for medicine and for the public, however, whatever Dr. Brown knew or suspected he imparted to his associates; therefore his work did not die with him.

As would be expected of a man of such brilliant mind and admirable social qualities, Dr. Brown was in great demand as a speaker at medical meetings. He traveled the country over, rapidly, for thousands of miles; yet he never seemed tired. Always he came back, clear-eyed, smiling, with a springy step.

Dr. Brown was short, erect, neat, blue-eyed, firm-

chinned, ruddy-faced, cheerful, tolerant, generous, frank, hospitable, a good fellow. He was, withal, brilliant, confident, a respecter but not a slave of authority, a dependable physician of seeking mind, and an excellent teacher and inspirer of others.

Elections to membership in medical organizations and other honors were bestowed on Dr. Brown. He was associate professor of medicine, The Mayo Foundation, Graduate School, University of Minnesota. He was Regent of the American College of Physicians for two terms, 1929 to 1933. He was a member of the Olmsted-Houston-Fillmore-Dodge County Medical Society, the Minnesota State Medical Association, the American Medical Association, the American Society for Clinical Investigation, the Association of American Physicians, the American Association for the Advancement of Science, the Central Interurban Clinical Club, the Central Society for Clinical Research, the Minnesota Society of Internal Medicine, the Minnesota Heart Society, the American Heart Association, Sigma Xi, Phi Rho Sigma, and the Association of Resident and Ex-Resident Physicians of The Mayo Clinic.

At the time of his death, which occurred in St. Mary's Hospital, Rochester, following an illness of two weeks, terminating in pneumonia, Dr. Brown was only fifty years of age. Mrs. Brown survives him. Also, one son, George, Jr., is a sophomore in the Medical School of the University of Michigan; the other son, Hugh, is a freshman in Carleton College.

George Everett Clark
1852-1935

DR. GEORGE E. CLARK of Stillwater died at his home August 26, 1935, at the age of eighty-three years.

George Everett Clark was born at Napoleon, Ohio, March 25, 1852. At the age of twelve he moved with his family to Adrian, Michigan, where he attended high school. He attended college at Kalamazoo, Michigan, and received his M.D. degree at Hahnemann Medical School in Chicago in 1880.

After practicing at Lima, Ohio, a few years, Dr. Clark moved to Stillwater, where he had practiced continuously until the time of his death. In January, 1891, he was appointed a member of the Minnesota State Board of Medical Examiners by Governor Merriam, a position he held until 1893, when he was appointed Professor of the Theory and Practice of Medicine at the University of Minnesota medical school.

An active member and deacon of the First Baptist Church of Stillwater, Dr. Clark served as active superintendent of the Sunday School until two years ago. He was a life member of the Baptist state convention and held various responsible positions in that organization throughout life.

Dr. Clark was a charter member of the St. Croix Lodge No. 14, A. O. U. W. In 1914 he was elected state medical examiner for the Minnesota grand lodge and in 1925 had conferred upon him the title of Past Grand Master Workman in recognition of his valued services.

Dr. Clark was married to Ella B. Bacon, December 27, 1880, at Putney, Vermont. He is survived by his widow and a cousin, Dr. G. W. Taft, president of the Northern Baptist Theological Seminary, Chicago.

E. Starr Judd
1878-1935

EDWARD STARR JUDD was one of those several sons of Minnesota who, reared where others had reached the heights of medical and surgical attainment, drew richly from his environment and then contributed abundantly in return. He was born in Rochester in 1878, the son of Mr. and Mrs. Edward F. Judd. He attended Rochester High School, and in 1902 he was graduated as Doctor of Medicine from the University of Minnesota. In 1902 and 1903 he served internship in Saint Mary's Hospital in Rochester. In 1903 and 1904 he was first assistant to Dr. Charles H. Mayo and in the latter year he became head of a section in the Division of Surgery in The Mayo Clinic. In 1915 he was appointed Associate Professor and in 1920, when he was forty-two years of age, Professor of Surgery, The Mayo Foundation, Graduate School, University of Minnesota. At the time of his death he was Chief of the Surgical Staff of The Mayo Clinic. His fame as a surgeon extended throughout the civilized world.

DR. JUDD

Although his training and experience qualified him for the broad designation of general surgeon, in his latter years Dr. Judd was engaged more in abdominal surgery than in other fields. Throughout the last two years of his life he devoted less of his time to operative surgery, more to consultation, and more to teaching, whereby he had prepared younger surgeons to take over his work. He had planned, during the coming year, to join Drs. W. J. and C. H. Mayo in their full time application to consultation and instruction.

In 1908, he first contributed to medical literature; his subject was inguinal hernia. From that time onward he was a constant writer on surgical subjects. In the early years his titles covered a wide range, such as cancer of the lip; skin grafting; operations for goiter, for diseases of the breast, and for conditions of the gallbladder; surgery of the urinary bladder and surgery of the kidney. After 1925, the bulk of Dr. Judd's contributions had to do with surgical disease of the stomach, intestine, liver, biliary tract, and pancreas. In all, about 325 articles under his name have been published.

Dr. Judd was in great demand as a speaker at medical meetings and many honors were bestowed on him. Throughout his life he was indefatigable in the work

of organized medicine, and in 1923 he was President of the Minnesota State Medical Association; in 1931 and 1932, long years of endeavor in the councils of the American Medical Association, culminated in his being elected its President. In 1932 he was President of the Society of Clinical Surgery, and in 1934 the University of Maryland admitted him to the degree of Doctor of Science. He was an honorary member of the Urologic Society of Brazil and a correspondent of the Royal Academy of Medicine of Rome. Dr. Judd was a member, also, of the Olmsted-Houston-Fillmore-Dodge County Medical Society, the Minnesota Pathological Society, the Minnesota Academy of Medicine, the Southern Minnesota Medical Association, the Interurban Surgical Association, the Southern Surgical Association and the Western Surgical Association. He was a member of the American Surgical Association, a Fellow of the American College of Surgeons, a fellow of the Seattle Surgical Society and an honorary fellow of the Philadelphia Academy of Surgery. In addition, he was a member of Alpha Kappa Kappa, of Sigma Xi, and of the Association of Resident and Ex-Resident Physicians of The Mayo Clinic.

Through the period of participation of the United States in the World War, Dr. Judd was Major, Medical Officers' Reserve Corps, and Director of the School of Instruction for officers of the Medical Corps and for enlisted men of the Medical Department of the Army, in Rochester. Thereafter he gave much time to training of medical reserve officers.

In person, Dr. Judd was a small man of might. He was noticeably erect, of stocky build, and a short neck bore a somewhat massive head. He moved briskly and purposefully. Just as there were no loose joints in his compact body there seemed to be no loose ends in his well ordered life. He did a tremendous amount of work without lost motion or lost words; yet he was not taciturn. He would talk freely enough, very much to the point, when he had anything to say. A somewhat impassive, extremely firm, but predominantly kindly face, with quiet, direct, clear gray eyes lay beneath a full brow. Here, the observer would say, is an imperturbable, energetic, effective, intelligent, practical, trustworthy man, who although of kindly disposition, is capable of impatience and of delivering rebuke if need be.

In 1908, Dr. Judd married Helen Berkman, of Rochester, the daughter of Dr. and Mrs. David Berkman. Of the five children, Eleanor, Mrs. O. L. Kirklin, lives in Rochester; Edward S., Jr., is a student in Rush Medical College; David is a student in the University of Minnesota Medical School, and Helen Phoebe and Mary Jane are attending Sweet Briar College in Virginia.

Dr. Judd left Rochester shortly before Thanksgiving Day, to address a meeting in Philadelphia, to see his daughters Helen and Mary Jane, and to attend the Army-Navy football game, for he had an abiding interest in athletics. He had a cold before his departure, but he did not consider it serious. He became definitely ill while passing through Chicago, where, in Presbyterian Hospital, he died of pneumonia on November 29.

Patrick Albert Smith

1866-1935

DR. P. A. SMITH was born in Nation Mills, Quebec, Canada, July 27, 1866, and died November 27, 1935, at the age of sixty-nine at Faribault.

Dr. Smith obtained his education in the Canadian public schools and graduated from Ottawa University in 1884 and from the Jefferson Medical College in 1893. In 1910 he took a postgraduate course in Vienna, Paris and London.

For several years Dr. Smith served as county coroner, resigning that position to become county commissioner. He was chairman of the county commissioners at the time of his death. Dr. Smith's tireless devotion was responsible for the erection of the new court house at Faribault, which is regarded as the finest in the state.

Dr. Smith served as county physician for a number of years and represented the county on the Cannon Falls Sanatorium board. At one time he acted as a member of the Advisory Commission of the Minnesota State Board of Control. He was a member of the Rice County Medical Society, State Medical Association and American Medical Association, the Lions Club, Order of Foresters, and the B.P.O.E.

In 1892 Dr. Smith married Lilas H. Brady of Montreal, Canada. Four children were born of this union. Mrs. Smith died in 1916 and in 1922 Dr. Smith married Loretta Lieb, who died the same year. He is survived by three sons, Ewart, Ardath and Verrill, and one daughter, Lilas.

Laurence F. V. Sutton

1879-1935

DR. L. F. V. SUTTON of Mazeppa, Minnesota, died very suddenly of a heart attack on retiring, December 4, 1935.

Laurence F. V. Sutton was born in Zanesville, Ohio, January 22, 1879, and received his common school education in Zanesville and Columbus. He studied at the University of Maryland and received his M.D. degree at the University College of Physicians and Surgeons at Baltimore in 1906.

Dr. Sutton began practice in Zanesville, Ohio, in 1906, but soon moved to Chicago, where he practiced from 1906 to 1916. He then became physician in charge at the Buena Vista Sanatorium at Wabasha, Minnesota. Later he located in Saint Paul and in 1917 he joined the Ramsey County Medical Society, but transferred his membership to the Wabasha County Medical Society in 1921, when he moved from Saint Paul to Mazeppa. In 1929 he again transferred his membership to the Olmsted County Medical Society, this society meeting in closer proximity to his location.

Dr. Sutton was local health officer at Mazeppa for many years. He was a member of the Masonic order as well as of county and state medical societies and the American Medical Association. Besides his widow he leaves a son, Carol, and a daughter, Marian. A man

of wide general culture and a skillful physician, Dr. Sutton will be greatly missed in the life of Mazeppa.

William P. Thelen
1876-1935

DR. WILLIAM P. THELEN died at the home of his brother, A. C. Thelen, near Washburn, Wisconsin, July 17, 1935, having been in ill health for a number of years.

William P. Thelen was born in 1876 on the Thelen farm near Houlton. He attended school at Stillwater and graduated from high school in 1897. He received his medical degree from the University of Minnesota and began practice at Carpio, North Dakota, later moving to Wilton, North Dakota, where he enjoyed an extensive practice.

For the past five years Dr. Thelen had spent his winters in Florida and his summers on the farm homestead near Houlton.

Dr. Thelen is survived by his widow (nee Mattie Bigler), a daughter, Mrs. Gretchen T. Newell of Chattanooga, Tennessee; one sister, Lucy Thelen of St. Joseph township; three brothers, Judge Edward Thelen of Stillwater, John Thelen of Great Falls, Montana, and A. C. Thelen of Washburn, Wisconsin.

Dinitrophenol Not Acceptable For N. N. R.

The Council on Pharmacy and Chemistry reports that, despite the warnings of investigators and a report issued by the Council, dinitrophenol has been used extensively in the treatment of obesity and not always with the necessary precautions. About twenty commercial concerns are furnishing dinitrophenol or mixtures in which this drug is the active principle. Some smaller concerns have sent samples of the drug unsolicited to physicians and in the accompanying literature have minimized the dangers of its use. It is not surprising, therefore, that undesirable and even serious toxic manifestations of the drug have been reported. Up to the present time six deaths following the administration of dinitrophenol have been reported. In most of the patients, death occurred within twenty-four hours of the onset of toxic symptoms such as dizziness, dyspnea, fatigue, pyrexia and excessive perspiration. The Journal has repeatedly indicated that the sale of dinitrophenol should be restricted to physicians' prescriptions and that the widespread use of the drug in the treatment of obesity should await further study in laboratories and clinics. The use of the drug should be limited to carefully selected cases. Patients with diabetes, nephritis and diseases of the liver and heart should not be given the drug. The Council has suggested that restrictions be placed on the sale of dinitrophenol and reducing mixtures containing dinitrophenol in this country and that the use of the drug be restricted to selected patients under the observation of properly trained physicians. The use of dinitrophenol by all others should await further careful experimentation in the laboratory. The Council voted that dinitrophenol and brands of dinitrophenol be not accepted for inclusion in New and Non-official Remedies and authorized publication of this report explaining its position in the matter. As the Council's report was going to press, reports were received of patients afflicted with cataract following the use of dinitrophenol. (J. A. M. A., July 6, 1935, p. 31.)

REPORTS AND ANNOUNCEMENTS OF SOCIETIES

Medical Broadcast for January

The Minnesota State Medical Association Morning Health Service.

The Minnesota State Medical Association broadcasts weekly at 10:00 A. M. every Monday over Station WCCO, Minneapolis and St. Paul (810 kilocycles or 370.2 meters).

Speaker: William A. O'Brien, M.D., Associate Professor of Pathology and Preventive Medicine, Medical School, University of Minnesota.

The program for the month will be as follows:

January 6—Fever Treatment.
January 13—Hysterical Paralysis.
January 20—Bronchiectasis.
January 27—Pyorrhea and Gingivitis.

The American College of Physicians

The twentieth annual session of the American College of Physicians will be held in Detroit with headquarters at the Book-Cadillac Hotel, March 2 to 6, 1936.

Dr. James Alex. Miller, of New York City, is president of the College, and has arranged a program of general scientific sessions of great interest to those engaged in the practice of Internal Medicine and associated specialties. Dr. Charles G. Jennings, of Detroit, is the general chairman of the session, and is in charge of the program of clinics and demonstrations in the hospitals, medical schools and other Detroit institutions. Dr. James D. Bruce, vice president in charge of university relations, University of Michigan, is vice chairman of the Committee on Arrangements, and has in charge the preparation of an all-day program to be conducted at the University of Michigan on Wednesday, March 4. Dr. Walter B. Cannon, Professor of Physiology at Harvard University Medical School, will deliver the annual convocation oration on "The Rôle of Emotion in Disease." Dr. Miller's presidential address will be on "The Changing Order in Medicine." About fifty eminent authorities will present papers at the general scientific sessions, while clinics and demonstrations will be conducted at the Harper, Receiving, Ford, Grace, Herman Kiefer and Children's Hospitals, of Detroit.

State Meeting

Plans for the 1936 meeting of the Minnesota State Medical Association took final shape at the second session of the Committee on Scientific Assembly held Saturday, December 14, in Saint Paul.

The state meeting will be held in Rochester, Monday, Tuesday and Wednesday, May 4, 5 and 6, at St. Mary's Hospital and Nurses' Home, with Council and House of Delegates meetings on Sunday, May 3.

By way of novelty, the demonstrations which have

been a feature of the past four meetings will give way, this year, to clinics. These clinics will be held each morning from 8:30 to 10:30 at St. Mary's Hospital by members of the Mayo Clinic Staff.

Addresses by out-of-state guest speakers will finish the morning sessions each day with a half hour reserved both morning and afternoon for viewing the exhibits.

The afternoon sessions, with the exception of the exhibit period, will be devoted to papers by Minnesota men.

A medical question court similar to those of the last two years will serve as a finale to the meeting Wednesday afternoon. This year, however, the questions will probably be confined to two or three selected subjects.

Two large evening meetings are planned, also, for Monday and Tuesday, May 4 and 5. The Monday evening meeting will be devoted to Medical Economics according to present plans. Dr. Olin West, manager of the American Medical Association, will be one of the speakers, also Mrs. J. W. Robb of Detroit.

A non-medical celebrity will be asked to address the Tuesday evening meeting if present plans go forward.

Technical exhibit space for this meeting is now at a premium, practically all spaces in the regular exhibit hall having been sold early in December. Additional spaces will be opened for a limited number of additional exhibitors in the corridors and in the East Hall of the Nurses' Home.

East Central Minnesota Society

The East Central Minnesota Medical Society held its annual meeting recently and elected the following officers: Dr. H. T. Norrgard, Milaca, president; Dr. Melvin Vik, Onamia, vice president; Dr. Elmer H. Hansen, Princeton, secretary-treasurer; Dr. C. G. Kelsey, Hinckley, delegate; Dr. H. C. Cooney, Princeton, alternate.

Dr. Everett C. Hartley of St. Paul talked at this meeting on "Clinical Observations on the Use of Endocrines in Obstetrics and Gynecology. Dr. Everett K. Geer of St. Paul talked on "Diagnosis and Treatment of Asthma" and Dr. R. G. Allison of Minneapolis on "Recent Developments in the Treatment of Malignancy by Deep X-ray Therapy."

Minnesota Radiological Society

The Minnesota Radiological Society held its winter meeting at the Nicollet Hotel in Minneapolis, Saturday, December 14th. The following program was presented:

Radiation Therapy of Carcinoma of the Lip—A. L. Abraham and W. K. Stenstrom, Minneapolis.

Roentgen Study of the Results of Epiphyseal Injuries—Oscar Lipschultz, Minneapolis.

The Dangers of Reducing Fractures Under the Fluoroscope—E. T. Leddy and C. A. Stevenson, Rochester.

Demonstration of Some Bone Changes in Children—M. J. Shapiro, Minneapolis.

Roentgen Study of Spontaneous Internal Biliary Fistula—C. N. Borman, Minneapolis.

Experiences with Roentgen Therapy of More Than 3000 R in One Month—W. K. Stenstrom and Lewis Jacobs, Minneapolis.

Combined Heat and Roentgen Therapy of Tumors—Review of the work of Stafford Warren and Associates—C. O. Hansen, Minot, N. D.

The next meeting of the Society will be held in St. Paul in March.

Minneapolis Surgical Society

January 9, 1936

Recreation Room, Nurses' Hall, University of Minnesota

9:30-11:30 A. M.

(Papers read to be limited to *ten minutes* only.)

DR. N. LOGAN LEVEN: Carcinoma of the esophagus

DR. HERBERT A. CARLSON: Surgical treatment of lung abscess

DR. DONALD CREEVY: Renal calculi

DR. MELVILLE H. MANSON: The Callander operation for amputation of the thigh

DR. OWEN H. WANGENSTEEN: The management of cases with imperforate anus

DR. LOUIS SPEILING: The rôle of the ileo-cecal sphincter in large bowel obstruction

DR. WILLLIAM T. PEYTON: Some experiences with mixed tumors of the palate and pharynx

DR. HARRY P. RITCHIE: Ten minutes of lantern slides of the face

11:45-1:15

Luncheon

University Hospital Staff Meeting

Dr. William A. O'Brien presiding

Subject for discussion: Empyema

1:30-5:00 P. M.

Operations by University Hospital Surgical Staff

Main operating room, fifth floor

8:00 P. M.

Regular meeting—20th floor, Medical Arts Building

DR. WILLIAM T. PEYTON: Report on brain tumor operations done at the University Hospital during the years 1935

DR. RALPH T. KNIGHT: Report from the Congress on Anesthesia

DR. OWEN H. WANGENSTEEN: The high gastric resection in cancer of the stomach with relation of personal experiences

All physicians are cordially invited to these meetings.

February 6, 1936

The Minneapolis Surgical Society will hold their 14th Annual Foundation Dinner on the evening of February 6, 1936, at the Minneapolis Club. Dr. Frank H. Lahey of Boston will give the oration in Surgery.

Representatives from the Chicago, Rochester, Duluth and Saint Paul surgical groups will be present and bring the greetings of these organizations.

Mower County Society

Mower County Medical Society held its annual meeting at the Hotel Austin in Austin, November 27. The following officers were elected: Dr. J. K. McKenna, Austin, president; Dr. J. M. Thompson, Brownsdale, vice president; Dr. P. A. Robertson, Austin, secretary, and Dr. A. E. Henslin, LeRoy, treasurer.

Range Medical Society

The monthly meeting of the Range Medical Society was held November 21, 1935, at Virginia. Drs. J. R. Manley and Philip Bray of Duluth spoke on the subject of Obstetrics. Dr. B. S. Adams of Hibbing gave a report of the recent meeting of the American College of Surgeons. Dr. S. S. Blacklock gave a short eulogy of the late Dr. Bullen of Hibbing.

Red River Valley Society

The following officers of the Red River Valley Medical Society were elected at the annual meeting of the society held on the evening of December 10, 1935, at Crookston, Minnesota: President, A. R. Reff, Crookston; vice president, J. L. Delmore, Roseau; secretary-treasurer, C. W. Froats, Thief River Falls; delegates, O. E. Locken, Crookston, and C. M. Adkins, Thief River Falls; censor for three years, A. M. Smith, Thief River Falls.

Washington County Society

At the annual meeting of the Washington County Medical Society the following officers were elected: Dr. George F. Brooks, Stillwater, president; Dr. V. C. Thompson, Marine, first vice president; Dr. Robert P. Ewald, Newport, second vice president; Dr. E. S. Boleyn, Stillwater, secretary-treasurer. Dr. Boleyn was elected State Delegate and Dr. Wade R. Humphrey, alternate. The censor for 1936-1939 is Dr. J. W. Stuhr.

Dr. Clarence N. Bulkley of Stillwater was elected to associate membership. Dr. Bulkley graduated from the University of Minnesota medical school in 1932.

A representative of the Woman's Auxiliary of Washington County Society reported the desire of the Auxiliary to coöperate with the county society, especially in connection with the sale of Christmas seals and high school debates on state medicine.

If you have not paid for your Christmas Seals, won't you do so now? Your help is needed.

WOMAN'S AUXILIARY

MRS. F. J. ELIAS, *President*, Duluth, Minn.
MRS. L. W. BARRY, *Editor, Press and Publicity*, 2193 Sargent Ave., St. Paul, Minn.

Hennepin County.—Completion of twenty-five years of organization of the Women's Auxiliary to the Hennepin County Medical Society was celebrated by a Silver Jubilee on December 6 in the Medical Library of the Medical Arts Building in Minneapolis. Twenty-five years ago a small group of wives of medical men, under the leadership of Mrs. W. M. Byrnes, conceived the idea of a medical auxiliary which would function as a social and philanthropic organization, the first of its kind in the United States. Today the group has a membership of 350 women, who, headed by Mrs. G. T. Nordin, are a very active and enthusiastic society. Mrs. J. M. Hall was in charge of the arrangements for the celebration.

The Women's Auxiliary to the Hennepin County Tuberculosis Association recently sponsored the sale of handwork of patients of Glen Lake Sanatorium. The entire proceeds of the sale, over $800, were turned over to the patients who made the articles.

Ramsey County.—The Auxiliary to the Ramsey County Medical Society reports that it exceeded its quota by 80 per cent in securing Red Cross memberships. Mrs. F. J. Plondke was in charge of this work.

The Ways and Means Committee, under the leadership of Mrs. Herman Kesting, arranged a very enjoyable and profitable Baked Ham dinner on December 11 in the Medical Rooms in the Lowry Building, Saint Paul. Dr. E. M. Hammes acted as toastmaster. A delightful program arranged by Mrs. K. C. Wold was enjoyed by over 200 guests. The proceeds from the dinner will be placed in the Emeritus Fund.

DERMAL ABSORPTION OF VITAMIN D

Several years ago, experiments on rabbits and rats were reported suggesting that Vitamin D was absorbed through the skin. Irradiated impure cholesterol suspended in cottonseed oil and applied to the depilated skin on the backs of the experimental animals completely protected them from rickets. Recently similar results have been obtained in rats administered viosterol by inunction. One investigator has observed that the application of viosterol in either a liquid petrolatum or a wax base to the tail alone permitted the absorption of sufficient amounts of the antirachitic factor to prevent the development of rickets. Further confirmatory evidence has been obtained on rats fed a standard rachitogenic diet and given inunctions of viosterol in an ointment base on areas of skin from which the hair had been removed by a sulphide depilatory. Both roentgenograms and "line tests" showed that the animals thus treated were completely protected from rickets, whereas controls receiving inunctions of irradiated liquid petrolatum developed the condition. The practical value of this method of administering Vitamin D remains to be determined. It may prove useful in infants and in subjects lacking the ability to utilize lipids administered orally. (J. A. M. A., July 6, 1935, p. 36.)

PROCEEDINGS *of the* MINNESOTA ACADEMY OF MEDICINE

Meeting of November 13, 1935

The regular monthly meeting of the Minnesota Academy of Medicine was held at the Town and Country Club on Wednesday evening, November 13, 1935. The President, Dr. A. R. Hall, called the meeting to order at 8 p. m. There were sixty members and one visitor present.

Minutes of the October meeting were read and approved.

Upon ballot the following men were elected as candidates for membership: Dr. W. L. Benedict, Rochester, to Associate membership; Dr. L. M. Daniel, Minneapolis, to Active membership; and Dr. Robert G. Green, Minneapolis, to University membership.

The scientific program followed.

RADIATION THERAPY

R. G. Allison, M.D.
Minneapolis

Dr. Allison read his Inaugural Thesis on the above subject and showed lantern slides. (To be published in full in Minnesota Medicine.)

Abstract

The history of radiation therapy was reviewed from the time of Roentgen's discovery of the ray up to the present time. The gradual evolution of the different measuring instruments was described. The development of the interrupterless transformer and the hot cathode tube was described. The combined radium-x-ray therapy was described. Comparative values of radiation at 200 kilovolts and 400 kilovolts and radium therapy were cited. The sensitivity of different types of tumors to radiation was discussed.

Discussion

Dr. R. T. La Vake (Minneapolis): Last year we had two cases of advanced carcinoma of the cervix and corpus uteri. One of these women in November of the year before came in with slight bleeding ten years after the menopause. She was told she must have a diagnostic curettage but she was going to Florida and said she would have it done there if necessary. After going to Florida she bled a little and the physician did not do a diagnostic curettage but gave her deep x-ray therapy (I do not know the strength) and she stopped bleeding. She came back in May and was apparently normal. About September she was brought in with a huge tumor that came up to the umbilicus. It gave the impression of being an ovarian cyst. A preliminary diagnostic curettage was performed. On going through a small senile cervix, a quart of bloody fluid came from the uterus and when the cervix was dilated a carcinoma was found which extended from the fundus of the uterus to and involving the cervix. It looked absolutely hopeless. Knowing that Dr. Schmitz had this 800 kilovolt machine, we sent her down to Chicago. That was last November, and when I examined her two weeks ago I could not feel the least bit of pathology. Apparently she is cured. Time alone will tell.

The other woman presented in extremis, but we decided to try the 800 kilovolt machine. So she was sent to Dr. Schmitz. She was almost moribund and we did not know whether she would live to get there. She had two courses of treatment and was well for about five months. Then she developed metastases and died in four months.

SCHLATTER'S DISEASE

L. C. Bacon, M.D.
Saint Paul

The treatment of three cases of Schlatter's disease or, as sometimes designated, Schlatter's syndrome during a period of one year, has caused me to view the difficulty with interest and to come to the conclusion that it is not as rare as the meager mention in textbooks would lead one to believe. In a rather extensive search of the surgical works in the English language, I find that reference to the condition is contained in a short paragraph or two or it is not mentioned. One surgeon of prominence devotes a short paragraph to the condition and states that he has seen such a case.

It is a difficulty of the adolescent period of life and in our cases occurred in high school athletes. The inference is that it may occur in the adolescent whenever the individual is subjected to a sudden and unprepared-for strain, especially in contests. Since seeing these cases I have taken the opportunity, when possible, to examine the tuberosity of the tibiæ in those with a history of youthful athletics and have been interested by the number who show an unusual prominence of the tuberosities. It seems probable that Schlatter's disease is more frequent than is supposed and that it is often overlooked.

Our cases gave a history of a sharp pain below the knee occurring during violent exercise, followed by continued pain and an inability to hold the leg stiff and to control the knee when standing. Grasping the tuberosities firmly between the thumb and fingers, they have been distinctly movable.

I have searched out the original discussion of the condition by Dr. Carl Schlatter, of Zurich, published in 1903, but have been unable to find a translation into English and it seems fitting that a translation should be here given. For this translation, I am indebted to the kindness of Dr. John J. Hochfilzer, of St. Paul. The discursive part of the original article follows, leaving out only the report of some eight cases.

(Translation)

Injuries of the Beak-like Process of the Upper Tibiæ Epiphyses

Dr. Carl Schlatter

"There is a typical form of a not very rare knee injury, but its clinical entity has not been fully described so far, in spite of the remarkable progress made in clinical diagnosis in the modern age. At least I

was unable to find any references in the medical literature.

"In such injuries a piece of bone is chipped off from the process of the upper tibial epiphysis, which embraces anteriorly, beak-like, the caput tibiæ.

"Among our large clinical material we see from time to time young patients who complain about pains in the knee region which they believe might have been caused quite some time ago either by trauma or spontaneously; physical findings in such cases are usually essentially negative except a tenderness over the tuberosities of the tibiæ; and so many times a wrong diagnosis has been made, calling this condition incipient tuberculosis of the tibial epiphysis or an inflammation of the infrapatellar bursa if a slight swelling in the region of the ligamentum patellæ accompanies the tenderness; but such a diagnosis becomes very doubtful after the patient has fully recovered in spite of no, or very irrational, treatment instituted for such conditions. Seven cases of this kind came under my observation in the last two or three years which were for a long time sailing under a wrong diagnosis. I succeeded finally in making a correct diagnosis in these cases. It was made possible through the coöperation of the x-ray institute of the Kanton Hospital in Zurich, whose chief is Dr. Zuppinger.

"The following up and study of these cases has finally convinced me that we are dealing with a very characteristic clinical entity and its symptoms can be interpreted quite easily even without x-ray pictures. (Then follows the report of eight cases.)

"First of all a few anatomical remarks which may illuminate the occurrence and etiology of these injuries. For the understanding of such cases it is of paramount importance to have an exact knowledge of the nature and development of the upper tibial epiphysis.

"The best textbooks of anatomy describe this condition very insufficiently and mostly in small print. It is said that, in adolescence, a tongue-like process develops at the proximal epiphysis from where the tuberosities of the tibiæ come off, but nothing is said about the very important question, in what year of development does this process appear and when does it disappear, that is, when does it unite with the diaphysis; also whether it originates from the epiphyseal plate or from a separate bone nucleus, or, in other words, whether it grows from above downward, or vice versa? According to Langer-Toldt, the development of the epiphyseal process occurs in the period from the eleventh to the thirteenth year, and disappears in the nineteenth year of life. According to Merkel-Heub, the unification between the epiphysis and the bone shaft takes place between the eighteenth and twenty-fifth years of life. Wilms and Sick studied the development of the bones on hand of numerous x-ray pictures from birth to full growth. They found, in the thirteenth year of age, the appearance of a beak-like process at the upper tibial epiphysis which later forms the tuberosity of the tibia. According to their observations the epiphysis united with the diaphysis in the twentieth year of age. Ludloff has lately written about the architecture of the lower epiphysis of the femur and upper end of the tibia. He states that a new seam of the epiphysis appears in the twelfth year of life, which branches off from the cross seam of the tibial epiphysis. In the seventh and eighth years of life this incipient stage of bone formation is hardly noticeable, but from then on it grows rapidly to a noticeable tuberosity in the fifteenth year of age and can not be distinguished from the diaphysis at the end of the eighteenth year of age.

"These classifications are of great importance in keeping before us the possibility of the occurrence of these injuries. I tried to substantiate the accuracy of these statements on a large amount of material at the institute of anatomy at Zurich. These investigations proved that the time of the appearance and disappearance of the epiphyseal process is very variable. In one case a fully developed process could be made out at the age of twelve; in another it could not be detected at the age of fifteen. It further proved that the unification of epiphysis and diaphysis may take place in some cases as early as the age of fourteen, while the usual time is between the eighteenth and twentieth years. From our x-ray pictures we formed the impression that not only general development and constitution, but also the race of the individual had a great influence on the growth of the epiphysis. For instance, we find an earlier differentiation of the epiphysis in the Roman race than in the Germanic.

"On close observation of our anatomical material and x-ray pictures we find, without exception, a bone nucleus at the distal point of the tongue-like process; this nucleus always has some connection with the process either through porous fragile bone substance or a small cartilaginous bridge, according to the age of the individual. Therefore, it is our belief that in the great majority of cases the epiphyseal process arises from the bone nucleus of the tuberosity of the tibia by a growing together of the nucleus and the epiphyseal plate. This point of conjunction leaves an area of diminished resistance where even slight injuries may cause a separation of the continuity. There we have, in the earlier years of life, a thin cartilaginous and later a fragile spongy bone (Spange) in the same area that the ligamentum patella is inserted and it is easily conceivable that, besides direct fractures, indirect fractures may occur through a forceful contraction of the quadriceps muscle. It is peculiar that in many cases of our material the patient denied any kind of trauma though the x-ray pictures gave definite proof of an injury to the epiphyseal process.

"A survey of our material relative to the pathological anatomical changes brings out the fact that the point of the epiphyseal process where the bone nucleus is located is usually the seat of the injury. We find this portion either in a state of dislocation or, later on, thickened by the formation of callus. During the developing stage of the process only its points seems to be subjected to injuries because the weak cartilaginous bridge is unable to transfer the force. In one macerated bone of a juvenile individual, I saw the formation of a fracture line just because of the process of maceration, but in the later stage of development, where the epiphyseal process is already united with the diaphysis, a dislocation of the whole beak-like process may take place. The ages of our patients were between the twelfth and seventeenth years. Individuals between thirteen and fourteen years of age seem to be especially disposed to this injury.

"Very peculiar was our observation that all cases were males and that the injury occurred seven times on the right knee and only once in the left. The reason for the rare occurrence among females may be the difference in their occupations and the less strenuous use of their muscles. I do not believe the fact that the right knee is so often involved is just accidental. There are certain reasons for this predisposition of the right side. Daily experience shows us that the right leg is much more used than the left, and therefore the musculature of the right extremity is better developed than the left one. The right extremity is therefore more often exposed to various insults and its strong quadriceps muscle may easily cause a tear of the ligamentum patella from its insertion and so lead to an indirect fracture.

"Now in regard to the symptoms of these injuries. The subjective symptoms have something very characteristic. We are usually dealing with male patients in the period from the twelfth to the twentieth years, but especially in the thirteenth and fourteenth years of age. Going into their history we find that their symptoms, chiefly pain in the knee region, were caused either by

a direct fall on the knee or by a forceful pull of the quadriceps muscle. These pains may be very light in the beginning so that the patient may have forgotten what caused them. In uncomplicated injuries of this kind the functional disturbances are very slight, and maximum flexion and extension are possible. Only in cases where the extremities are used a great deal the pains may exacerbate. Frequent recurrences of these increased pains may finally bring the patient to the physician although the injury may have occurred many months in the past.

"Among the objective symptoms, the most characteristic is tenderness on pressure over the epiphyseal process. The typical tender spot lies over the tuberosity of the tibia about two and a half centimeters below the knee joint. The region of tenderness can be covered with the end of your thumb. Besides this tenderness, one usually finds, on the same spot, a bony protuberance. If the patients are examined in the later stage of their morbidity, these two symptoms only are markedly pronounced. If the injury is a recent one, one finds also a swelling of doughy consistency in the patellar region. The knee joint itself is usually free from symptoms if the injury is uncomplicated and so extra-capsular. Another symptom which should be mentioned is the muscular atrophy, especially of the quadriceps muscle, because of the inactivity of the lower extremity.

"The prognosis of this condition is favorable. We are dealing with an affection which is part of a physiological development of the bone, and which disappears as soon as a bony union between epiphysis and diaphysis has taken place. Therefore time itself may bring complete recovery without any medical intervention. The closer the patient is to the end of the developing period, the sooner will the morbidity cease; therefore the prognosis is more favorable in older individuals than in younger ones. Involvement of the knee joint has a great influence in determining the time of recovery.

"Of great importance is an early rational treatment. These cases without treatment suffer pains over a period of a year or more, while the treated cases were much sooner relieved of their pains, some even after a few weeks. In spite of the long period of morbidity, no permanent disability results from it. Sometimes the formation of marked callus at the tuberosity of the tibia may develop, which hinders long kneeling on the knee. The principle of a rational treatment for these cases is immobilization of the knee joint. If the injury is of slight degree application of an immobilizing bandage is sufficient. Severe cases demand rest in bed that will also help to prevent further action of the quadriceps muscle on the plane of fracture. Starch bandages are better than splints. It is advisable to start with massage of the quadriceps muscle quite early to prevent an otherwise inevitable muscular atrophy."

This ends the translation of Dr. Schlatter's article, and the most that can be said about these cases has been discussed therein; but in our cases we noted a few variations.

In all three of our cases the tuberosities of both tibiæ were fractured. In all three cases the onset of the difficulty was marked by a sharp pain followed by continuous pain and inability to control the knees. The patients said the knees became weak at once and continued weak. The trouble began during strenuous exercise and had existed only a few days when we were consulted. The pain and swelling were confined to the area of the tuberosities and these were prominent and distinctly movable when firmly grasped between the thumb and finger.

The first case was in a large and finely developed boy, aged fifteen years, who played center on one of our high school football teams. The pain and disability came on during a scrimmage. He had completely lost the ability to extend the legs and to control them when standing. As you can see in the x-ray negative, the insertion of the patellar tendons with a portion of the tuberosities had been torn away and a dislocation of the remainder of the tuberosities had occurred.

The second case was that of a fifteen year old boy whose specialty was pole vaulting. The detachment was not as complete as in the first case, but was of the lower portion of the tuberosities with fracture through the process, and the disability was not as great as in the first case.

The third case was that of a ten year old girl given to doing cart-wheels. Both tuberosities were displaced and the general symptoms were the same as in the other cases. This case showed exceptions to several of Schlatter's observations, namely, a girl and younger in age. The fact that she was athletic makes it probable that the difficulty may occur in either sex if the properly directed strain occurs. As you will see in the negatives, the rupture is marked in the first view; in the second, taken after four weeks, the position is good and the line of cleavage is still apparent. The third plate, taken nearly a year later, shows the final results. The left still shows the line of cleavage with some bone formation making a firm union. The right seems to be united by bony formation. The child has just reached her eleventh year.

We saw all of these cases within a few days of the accidents and the symptoms were acute and apparent. Rest, posterior splints and strapping with adhesive, corrected the symptoms in a few weeks, with a restoration of function. In all cases the tuberosities remained prominent.

Discussion

DR. A. R. COLVIN (St. Paul): The changing opinion relative to the etiology of bone disease is interesting to follow. It is but a short time since there was a great deal of speculation as to the origin of von Recklinghausen's disease or generalized osteitis fibrosa; and then out of the researches on parathyroid disorder and calcium regulation comes the recognition of the relationship of parathyroid tumors to hyperparathyroidism and the relation of this to decalcification of bones and to osteitis fibrosa. Removal of the parathyroid tumor results in complete calcification of the bones again.

In 1903 Schlatter described a traumatic separating of the epiphysis of the tibial tubercle. Osgood described it in 1904, and in 1906 Schlatter again described partial separation of the tubercle. In 1917 and since there seems to be a tendency to include Osgood-Schlatter's disease in the same category as Perthes, Calve, Legg disease of the hip in the young and it is now designated as Osteochondritis Deformans Juvenilis. This disease process seems to begin in the bone underlying the epiphyseal cartilage with a resulting separation of the epiphysis due to trauma or not, for there often is no history of trauma. Osteochondritis dissecans used to be ascribed to trauma, and here again we have an

underlying circumscribed osteitis with resulting fracture of the cartilage and the letting free of a loose body in the joint.

The two slides I have are shown to indicate the importance of differential diagnosis in the region of the tibial tubercle. The first slide shows a localized granulating osteitis in the region underlying the tubercle; from the granulation tissue cultures of staphylococci were found. In the slide it looks as if the tubercle had been separated.

In the next slide, a small area about the size of a grain of wheat is seen on the superficial surface of the tubercle from which again cultures of staphylococci were made. These slides are shown, not to connect them with Schlatter's disease, but to call attention to the diagnostic possibilities. Perthes, Calve, Legg disease, Schlatter's disease, Kohler's disease, are also spoken of as an osteochondritic dystrophy.

Dr. Arnold Schwyzer (St. Paul): This paper brings back memories of student days. Schlatter and I were students together and were for a short time together as assistants of Kroenlein in Zurich. Schlatter, in Kroenlein's absence, made the first successful total gastrectomy. When he later came out with his observations on what he termed avulsion of the tuberculum tibiæ he considered the condition due exclusively to trauma. However, right from the start this explanation did not satisfy others. Roentgenologists showed that what he had taken for an avulsion of the tubercle could be seen rather regularly in adolescents, particularly in late rickets. It was then shown that quite often trauma had not preceded, and that in some cases the trouble was bilateral.

The tuberculum has a separate center of ossification but is connected with the cartilaginous line of growth by hyalin cartilage. Thus the slender shadow appears torn away from the tuberosity, but in reality is connected by cartilage. Nevertheless, Schlatter has called attention to a well localized disturbance which at times is due to trauma. It was later found that the great majority of the cases with this localized pain, swelling and an abnormal x-ray finding of the tuberculum, are occurring on the soil of late rickets. I remember a bilateral apophysitis of this kind where positively no trauma had preceded as far as the intelligent patient could remember. There was a well localized swelling and pain and the typical x-ray finding. No further treatment was necessary beyond abstaining from harsh exercise.

As all apophyses grow by endochondral ossification, disturbances in the deposition of lime salts will occur. These disturbances are not as great as on the ends of the diaphyses (the metaphyses) because the growing activity is, of course, much less in the former. Nevertheless, disturbances do occur often because the bones near the joints are more superficial and more exposed to trauma. Irregularities in the ossification of the tibial tubercle are of numerous shapes and the exposed location easily leads to mild forms of inflammation.

Dr. C. C. Chatterton (St. Paul): We see a great many cases of painful knees in children along about "marble time," that is, when boys and girls are playing marbles on frozen ground or cement walks, and very often if an x-ray picture is taken we find that the tuberosity of the tibia is apparently loose, often in many pieces or fragmented. These cases primarily recover by simple supportive treatment with a bandage and pad over the knee. We very frequently find a similar condition, as far as the x-ray is concerned, in normal individuals. When the tuberosity of the tibia becomes infected, it certainly demands more than the usual protective treatment and practically always an operation is necessary to remove any dead bone or curette the granular area between the tuberosity and the shaft of the bone, removing the area of infection and allowing the tuberosity to become united with the shaft of the tibia.

Dr. Bacon (in closing): I want to thank the gentlemen for their discussion. It has been very interesting to me.

The problem that came to my mind was that while my cases were distinctly traumatic and healed very promptly with rational treatment, I wondered why they sustained separation of both tuberosities instead of only one as described by Schlatter. It seems to me there must have been some nutritional deficiency, as suggested by Dr. Colvin.

I have been particularly interested, since seeing these cases, in examining the tuberosities of the tibiæ in high school athletes, and to note the frequency with which sharply prominent tuberosities appeared. To me this would indicate that there had been some injury sustained.

ERYSIPELOID INFECTION FOLLOWING AN ABRASION

John C. Brown, M.D.,
Saint Paul

While cleaning up a Buffalo skull the knuckle on my right index finger was scuffed. It was thoroughly washed at once but it could not be made to bleed. Alcoholic solution of merthiolate was applied and the hand was bandaged.

The second day the knuckle swelled some and two red spots appeared on each side of the distal part of the joint followed by a similar pair on the proximal side on the same joint. Wet dressings were applied but additional paired spots both distally and proximally to the spots already found appeared. These spots were all alike in character and were not raised above the adjacent skin. They were red to wine colored and in none became confluent with each other. At this stage light treatments were started and at first seemed to slow up the process, but after about the third week the finger and joint began to swell and was very painful. When this was noted it was decided to give it an x-ray treatment. This was given at about 12 o'clock on Sunday. By the time I got home there was no pain in the joint and by the next day the swelling had gone and the spots were bleaching out. About four days after the first treatment it was thought best to give it one more exposure to the x-ray. This was done and the condition had cleared up in less than a week. Cast 3 represents the fulminating stage just before the first x-ray treatment. There was another peculiar thing noticed. This hand had a considerable blotching of vitiligo and all of the erythematous patches avoided these areas and were found only on the normally pigmented portions of the skin. There was no temperature at any time and only slight anesthesia and stiffness at the time of swelling just before x-ray treatments. Dr. Colvin examined the finger first and then turned me over to Dr. Madden for light treatment.

The meeting adjourned.

R. T. LaVake, M.D.,
Secretary.

BOOK REVIEWS

Books listed here become the property of the Ramsey and Hennepin County Medical libraries when reviewed. Members, however, are urged to write reviews of any or every recent book which may be of interest to physicians.

FOR AND AGAINST DOCTORS. Compiled by Robert Hutchison and G. M. Wauchope. 168 pages. Price, cloth, $2.00. Baltimore: William Wood & Co., 1935.

NEW PATHWAYS FOR CHILDREN WITH CEREBRAL PALSY. Gladys Gage Rogers and Leah C. Thomas, of Robin Hood's Barn. 167 pages. Illus. Price, cloth, $2.50. New York: The MacMillan Company, 1935.

COMPLETE HANDBOOK ON STATE MEDICINE. J. Weston Walch, Chief Compiler. 158 pages. Price, paper cover, $2.50 for first copy, 75c each for additional copies to same school. Portland, Maine: Debaters Information Bureau, 1935.

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IMMUNOLOGY. Noble Pierce Sherwood, Ph.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kansas. 608 pages. Illus. Price, cloth, $6.00. St. Louis: C. V. Mosby Co., 1935.

INFANT NUTRITION. Williams McKim Marriott, B.S., M.D., Professor of Pediatrics, Washington University School of Medicine, Physician in Chief, Saint Louis Children's Hospital, Saint Louis. 431 pages. Illus. Price, cloth, $4.50. St. Louis: C. V. Mosby & Co., 1935.

THE HUMAN FOOT. Dudley J. Morton, Assoc. Professor of Anatomy, College of Physicians and Surgeons, Columbia University. 244 pages. Illus. Price, cloth, $3.00. New York: Columbia University Press, 1935.

THE 1935 YEAR BOOK OF GENERAL MEDICINE. Edited by George F. Dick, M.D., et al. 848 pages. Illus. Price, cloth, $3.00. Chicago: Year Book Publishers, 1935.

COMPLETE HANDBOOK ON STATE MEDICINE.

J. Weston Walch. 158 pages. Price $10.00. Portland (Me.): Debaters' Information Bureau, 1935.

This large paged volume is published for the assistance of the debater on either the affirmative or negative side of the question of the advisability of the adoption of state medicine.

The volume is devoted to chapters on how to approach the study of the question, the preparation of affirmative or negative briefs and rebuttal notes. It consists largely of innumerable quotations from as many writers and should prove to be a valuable aid to debaters on the subject.

BEHAVIOR DEVELOPMENT IN INFANTS.

Evelyn Dewey. 304 pages. Price, $3.50. New York: Published for the Josiah Macy, Jr., Foundation, by Columbia University Press, 1935.

This is a survey of the current literature since 1920 on growth processes and infant behavior during the fetal period and the first two years of postnatal life, according to the plan being followed in the study of growth by the Normal Child Development Clinic of the Neurologic Institute of New York City. "Behavior" is defined as the neuromuscular and glandular reactions of living human organisms. Because social and emotional developments involve interpretations which lead afield into theoretical speculations, the scope of study was restricted; and there is yet, it is asserted, no satisfactory theory of the processes underlying strictly objective neuromuscular behavior patterns. Two current theories of growth processes are those of the biologists and those of the psychologists; objective evidence for the former is based on neurophysiologic data on the correlation of structure and function, and for the latter on human and animal behavior. The biologist—or neurophysiologist—has been handicapped in that his studies have been mainly concerned with animals. The point of view of "growth process," rather than performance at successive age levels, has been adopted.

The development of scales for measuring intelligence and the normal growth increments and the advances in the sciences of neurology and physiology are responsible for the great impetus to investigation of infant behavior. Clinical practice has profited by the establishment of norms obtained by observation of the behavior of groups of babies and simple tests at stated age periods from birth on.

The review indicates that methods of studying behavior and its specific patterns have made great strides in objectivity, in accuracy and in the quantity of results. However, it shows also that there is still a break between the fetal, the neonatal, and later period of development. And behavior patterns have not yet been followed sequentially from their inception to their fully developed form.

It appears generally accepted that the development of behavior follows, or is coordinate with, the development of neural structures. There continues controversy about the relative rôles of the environment and the innate neural matrix in controlling development. Instinct and learning are now regarded as parts of a continuous process of development, occurring, if not brought about, through the interaction of the environment and the organism. Two schools of psychology,

the behaviorists and gestaltists (configurationists) support differing views of behavior development. The former hold that "consciousness," or a mental factor in behavior, must be ruled out and that all accounts of behavior be made in simple mechanistic terms of stimulus response. The latter school denies instincts, it postulates a fundamental organization of the nervous system which serves to give the organism a certain very simple adaptation to the environment from the beginning. The tendency is now to discard the former, the older reflex-arc theory, and to support the gestalt or organismic conceptions of growth processes, and to emphasize with the neurophysiologists, in particular, that maturation of neural structures, at least to a certain degree, must exist before functioning occurs; to them growth in structure and its use are interdependent, each reacting upon and stimulating the other.

The text, published by the Columbia University Press, refers to prior contributions by Columbia investigators and to investigations reported from many countries, indeed to a bibliography of 216 publications listed at the end of the book.

JOSEPH C. MICHAEL, M.D.

Oral Immunization to Colds

For the last two winters, investigators have been studying the efficacy of an orally administered heterophile antigen vaccine in reducing the incidence of the common cold. The strains of common respiratory organisms used in the vaccine were selected for heterophile content and ability to resist the effects of gastrointestinal secretions. The organisms contained in each capsule were: pneumococci, 25 billion; Hemophilus influenzæ, 5 billion; streptococci, 15 billion, and Micrococcus catarrhalis, 5 billion. The effectiveness seems to have been judged by the average number of colds occurring in the vaccinated group when compared with their average during the preceding three years and with "controls" not taking the vaccine. Aside from the theoretical objections to oral vaccination for colds, many of which are obvious, there are some specific reasons against the acceptance of this work as adequately controlled. For example, the group taken as controls had, in all instances previous to the experiment, a lower average number of colds per season than the vaccinated group. Furthermore, in view of the known factors of age, exposure and tremendous variation in colds from season to season and in different locations, any yearly variation in cold morbidity in one location or in small groups is of small utility as scientific evidence. The reports of the therapeutic value of orally administered "cold" vaccines are hardly convincing. (Jour. A. M. A., September 7, 1935, p. 804.)

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